Experimental Research

The effects of anastrozole on neonatal rat skin

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Summary

Background: Anastrozole is a third-generation nonsteroidal aromatase inhibitor which is used in the treatment of breast cancers. Anastrozole has also been used in the treatment of dermatomyositis skin eruptions but its direct effects on skin have not been well documented. *Objective:* To study the effects of anastrozole administration on neonatal rat skin. *Methods:* Forty Spraque-Dawley female newborn rats were separated into two control groups and two experimental groups (n = 10). One day after birth the control group of newborn rats were given daily 0.02 ml saline subcutaneously for a period of 15 days. The first experimental group of rats were treated with 0.05 mg/100g/day anastrozole subcutaneously for 15 days wheras the second experimental group of rats were given 0.25 mg/100g/day anastrozole subcutaneously for 15 days. Histopathological assessments were made and compared with the control groups. *Results:* Increased keratinization, strippling, hypertrophic epidermal cells and disorganization of the epidermal cells were observed in the first experimental group. In the second experimental group in addition to these pathologic findings acantholysis was observed. *Conclusion:* The administration of anastrazole in newborn rats showed considerable harmful effects.

Key words: Anastrazole; Rat; Skin.

Introduction

Tamoxifen, a non-steroidal antiestrogen drug, has been the mainstay of hormonal therapy in breast cancer. In a previous study, some abnormal findings were observed in the skin of rats with tamoxifen administration after birth [1]. Third-generation aromatase inhibitors (AIs), anastrozole, letrozole and exemestane are effective and well-tolerated as adjuvant therapy. These AIs induce remissions in a significant proportion of of postmenopausal patients with estrogen-receptor-positive breast cancer [2-4]. Anastrozole has also been used in dermatological practice in the treatment of dermatomyositis skin eruptions [5].

The effects of anastrozole administration on skin has not been well documented. The present study was undertaken to determine the skin effects of aromatase inhibitor anastrozole in newborn mice.

Materials and Methods

Rats were caged and fed standard pellet food during the study and kept under controlled

temperature conditions at a constant day/night cycle. Forty Spraque-Dawley female newborn rats were separated into four groups (n = 10), two control groups and two experimental groups. One day after birth, both control groups of newborn rats were given 0.02 ml saline daily subcutaneously for a period of 15 days. The first experimental group of rats were treated with 0.05 mg/100g/day anastrozole subcutaneously for 15 days whereas the second experimental group of rats were given 0.25 mg/100g/day anastrozole subcutaneously for 15 days. The control and experimental groups of rats were anesthetized at the end of the 15 days. Several biopsies were taken and fixed in a solution of 10% formaldehyde. The tissues were then embedded in paraffin wax, sectioned and stained with hematoxylin-eosin (H&E). Histological assessments were performed and compared with their control groups using a light microscope. The study was approved by the Local Ethics Committee.

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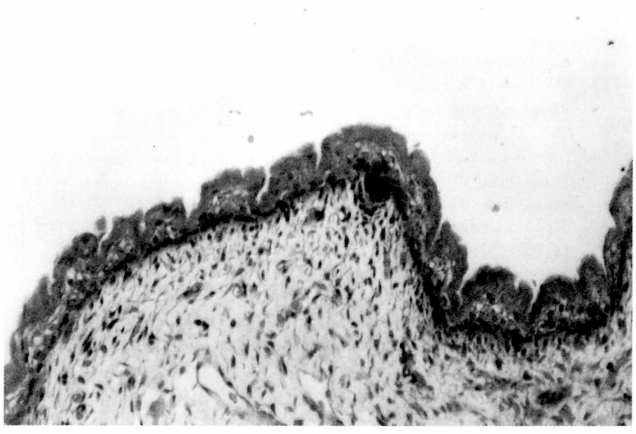
Results

Increased keratinization, hypertrophic epidermal cells, disorganization of the epidermal cells and strippling were observed in the first experimental group (Figure 1). Normal arrangement of the basal layer cells and dermis was observed in the first control group of rats (Figure 2). Increased keratinization, hypertrophic epidermal cells, disorganization of the epidermal cells and strippling were observed in the second experimental group. However, the most stiking changes were acantholysis (Figure 3). Normal arrangement of the basal layer cells and the dermis was also observed in the second control group of rats. Impaired skin maturation was observed with anastrazole administration in both experimental groups (Table 1).

Table 1. — *Histopathological findings in both experimental groups.*

Histopathological findings	First experimental group (n = 10)	Second experimental group (n = 10)
Increased keratinization	10	10
Hypertrophic epidermal cells	10	10
Disorganization of epidermal cells	7	10
Strippling	7	10
Acantholysis	0	7

Fig. 1



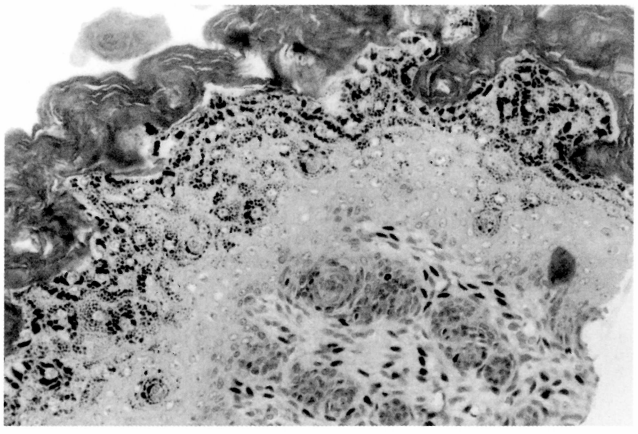


Fig. 2

Fig. 3

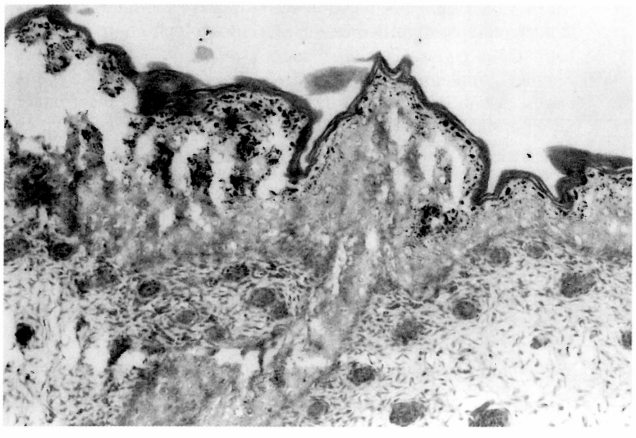


Figure 1. — Normal epidermis and arrangement of the basal cells in the first control group (H&E x 200).

Figure 2. — Increased keratinization, hypertrophic epidermal cells, disorganization of the epidermal cells and strippling in the first experimental group (H&E x 200).

Figure 3. — Increased keratinization, strippling of hypertrophic epidermal cells, and disorganization of epidermal cells together with acantholysis in the second experimental group of rats (H&E x 200).

Discussion

Although estrogens have a potent physiological role in numerous processes, they have crucial roles in pathological states like mammary and endometrial carcinomas. Breast cancer is one of the leading causes of death in middle-aged women and especially postmenopausal patients have estrogen-dependent breast cancer which needs estrogen for tumoral growth [6]. Aromatase is a cytychrome P450 enzyme complex which catalyzes the terminal step in the biosynthesis of estradiol thus making it a favorable target for the inhibition of estrogen [7]. The literature reports are in agreement with the high levels of aromatase in tumors compared to normal tissue [6]. Anastrozole is a third-generation nonsteroidal aromatase inhibitor producing approximately 97% inhibition of estrogen biosynthesis at a dose of 1 mg/d [8]. Phase III trials and several studies have shown anastrozole to be at least as effective as tamoxifen (TX), and was well tolerated as a first line therapy [6, 9, 10].

Antiestrogen drugs are indicated in several dermatological diseases. TX has been given in the treatment of several dermatological disorders such as malignant melanoma, autoimmune progesterone dermatitis, and desmoid tumors [11-14] while anastrozol has been used in the treatment of dermatomyositis skin eruptions [5].

TX administration was investigated in an experimental study; abnormal hair follicles, epidermal atrophy together with increased dermal fibrosis, and lymphohistiocytic inflammatory cell infiltration prominent around the hair follicles were observed in rats [1] In another study the potential of TX as an inhibitor of wound contraction was demonstrated in the treatment of abnormal dermal scarring [15].

The long-term effects of aromatase inhibitors (anastrazole, letrozole, exemestane) have been limited to trials with follow-up periods of five years or less. Hot flushes and musculoskeletal complaints/arthralgia are the most commonly reported adverse events associated with aromatase inhibitor therapy. Aromatase inhibitor therapy can also cause loss of bone mineral density and increased incidence of fractures. Negative effects on cardiovascular health, specifically on lipid metabolism, have been studied but not conclusively demonstrated [16-18]. There have been reported cases of cutaneous vasculitis related to short-term treatment with anastrozole for breast cancer. After anastrozole treatment was stopped, in both cases purpuric papules, skin ulceration and edema disappeared within two weeks, without any additional treatment [19, 20].

Conclusion

We observed that anastrozole interfered with the skin maturation of newborn rats. Antiestrogens are known to inhibit endothelial cell growth stimulated by angiogenic

growth factors and the impaired skin maturation may be related to the antiangiogenic action of the antiestrogens [1, 21, 22].

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