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An update on non-gynaecological effects of SERM's and aromatase inhibitors

C. Netelenbos*

Department of Endocrinology, Academic Hospital of Vrije Universiteit Medical Centre, PO Box 7057, 1007 MB Amsterdam, The Netherlands

The steroid hormone oestrogen influences the growth, differentiation and function of peripheral tissues of the reproductive system such as the mammary gland, uterus, vagina, ovary, testis and prostate. Oestrogens also have general metabolic roles that are not directly involved in reproductive processes. These include bone epiphyseal closure in puberty and bone turnover during lifetime, as well actions on cardiovascular tissue, lipids, carbohydrate metabolism and cerebral functioning in both sexes.

Most of the effects of oestrogen are believed to be mediated by genomic pathways involving the interaction of oestrogen with a nuclear oestrogen receptor (ER). An alternative non-genomic pathway has also been suggested following recently discovered putative cell membrane recognition sites.

Oestradiol production is not only an endocrine product of the ovary but is also produced in many other tissues. Those tissues have the capacity to synthesise oestrogens from androgen and to use oestrogen in a paracrine or intracrine fashion. There is increasing evidence that in both men and women extra glandular production of C(18) steroids from (C19) precursors by the enzyme aromatase is important in normal physiology, as well as in pathophysiological states. Aromatase is found in a number of human extra genital tissues, such as fat, bone, blood vessels and brain tissue.

Anti-oestrogens can be found in substances which block or modulate more or less selectively the oestrogen receptor (selective oestrogen receptor modulators; SERMs) or in substances that block the synthesis of oestrogen (aromatase inhibitors). In addition, phyto-oestrogens and oestrogen disruptors such as plastics dichlorodiphenyltrichloroethane (DDT), polychlorinated biphenyl (PCB) can also be considered as SERMs.

In the postmenopausal period, oestrogen production is totally dependent on the conversion of C19 to oestrogen. In elderly men, the converted oestrogen from testosterone appears to be more important in determining bone status than testosterone. Very recently, indications were found that aromatase gene polymorphism plays a role in postmenopausal osteoporosis.

Many different aromatase inhibitors are known and used in advanced breast cancer patients. In principle, it should be possible to develop selective aromatase modulators (SARMs) that block aromatase expression in selected tissues; for example, in breast, but allow unimpaired oestrogen synthesis in other tissues such as bone.

From the statements above, it becomes clear that use of SERMs or aromatase inhibitors both decrease circulating oestrogen levels and thus can have unwanted effects on other tissues than those to which they are directed. However, SERM's can also have wanted and unwanted oestrogenic effects (positive effect of raloxifene on bone and negative effect of tamoxifen on endometrial tissue, respectively) or wanted and unwanted anti-oestrogenic effects (effect of tamoxifen in premenopausal women in the prevention of breast cancer, but decreasing bone mineral density, respectively).

1. SERMs

Both tamoxifen and raloxifene are anti-oestrogenic in the breast, but oestrogen-like in the bone of postmenopausal women and reduce circulating cholesterol levels. SERMs also have different degrees of oestrogenicity in the uterus. Tamoxifen is specifically used to reduce the incidence of breast cancer in pre- and postmenopausal women at risk for this disease. Raloxifene, however, is specifically used to treat postmenopausal vertebral osteoporosis. At this moment, both drugs are compared in reducing breast cancer incidence in high-risk postmenopausal women Study of Tamoxifen And Raloxifene (STAR trial).

In postmenopausal women, the principal positive action of oestrogen supplementation is to alleviate menopausal symptoms and mood changes. Other

* Tel.: +31-20-444-0530; fax: +31-20-444-0502.
E-mail address: c.netelen@vumc.nl (C. Netelenbos).

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positive actions are the inhibition of postmenopausal bone loss and favourable effects on risk factors of coronary heart disease. However, negative actions of oestrogen are an increased risk of endometrial and breast cancer, while also negative reports about the secondary prevention of coronary heart disease have been published recently. These negative effects makes oestrogen supplementation for chronic use a less constructive form of treatment for aging women. Ideally, SERMs could be a better alternative to enhance positive oestrogenic effects in the central nervous system, eliminating hot flushes, preventing coronary disease, osteoporosis, breast cancer and endometrial cancer, and avoiding thromboembolic disorders. Tamoxifen and raloxifene also do not fulfil the criteria for an ideal SERM. However, new SERMs are being developed as coactivator and corepressor proteins that modulate the ER in target cells which could be more ideal substances for aging women.

2. Aromatase inhibitors

Low to very low oestrogen levels in postmenopausal women are associated with a lower bone mass. Long-term treatment with aromatase inhibitors will therefore induce bone loss. The combination of an luteinising hormone-releasing hormone (LHRH) analogue with an aromatase inhibitor can induce a profound oestrogen suppression in premenopausal breast cancer patients causing elevated bone turnover, but the few literature reports show in the short run that there were no deleterious effects on bone status. However, from a theoretical point of view, it would be wise to add bisphosphonate treatment to this combination, especially when the bone mass is already low.

A significant decrease in serum oestradiol levels paralleled a significant increase in total cholesterol, low density cholesterol and apolipoprotein B blood levels in women with metastatic breast cancer treated with letrozole, a potent selective aromatase inhibitor.

One can expect cognitive problems because of lowering oestrogen levels. However, no clinical data are available. Brain aromatase appears to be neuroprotective from studies in an experimental animal model. The aromatase inhibitor enhanced neurodegeneration in the hippocampus of intact male rats and this was counterbalanced by oestradiol administration.

The combination of an aromatase inhibitor with a SERM can diminish the potential negative effects of an aromatase inhibitor in postmenopausal women resulting in more favourable effects on bone and lipids, and also the uterus, when raloxifene is used.