Biological effects of progestins in breast cancer.

Source: Hormones and Cancer Research Unit, Paris, France.

Developments in the synthesis of different progestins have opened up new possibilities for the biological effects and therapeutic uses of these compounds. The actions of progestins are a function of their structure, affinity to the progesterone receptor or to other steroid receptors, the target tissue considered, the biological response, the experimental conditions, dose, and metabolic transformation. Data on the action of progestins in breast cancer patients are very limited. A positive response with the progestins medroxyprogesterone acetate and megestrol acetate has been obtained in postmenopausal patients with advanced breast cancer. However, extensive information on the effect of progestins was obtained in vitro studies using hormone-dependent and hormone-independent human mammary cancer cell lines. It was demonstrated that in hormone-dependent breast cancer cells, various progestins (nomegestrol acetate, medrogestone, promegestone) as well as tibolone, are potent sulfatase-inhibitory agents. Progestins may also be involved in the inhibition of the mRNA of this enzyme. In another series of studies, it was also demonstrated that various progestins are very active in inhibiting the 17 beta-hydroxysteroid dehydrogenase for the conversion of estrone to estradiol. More recently, it has been observed that promegestone or medrogestone stimulates the sulfotransferase for the formation of estrogen sulfates. Clinical trials of these enzymatic effects on the formation and transformation of estradiol in breast cancer patients could be the next step to investigate new therapeutic possibilities for this disease.

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The action of progestins is derived from many factors: structure, affinity for the progesterone receptor or for other steroid receptors, the target tissue considered, the biological response, the experimental conditions, the dose and metabolic transformation. The proliferative response to progestins in human breast cancer cells is contradictory: some progestins inhibit, others stimulate, have no effect at all, or have a dual action. For instance, medroxyprogesterone acetate has a stimulatory effect on breast cancer cells after a short period of treatment, but this effect becomes inhibitory when treatment is prolonged. It has been demonstrated that, in hormone-dependent breast cancer cells, various progestins (nomegestrol acetate, medrogestone, promegestone) are potent sulfatase inhibitory agents. The progestins can also involve the inhibition of the mRNA expression of this enzyme. In another series of studies it was also demonstrated that some progestins are very active in inhibiting 17beta-hydroxysteroid dehydrogenase for the conversion of estrone to estradiol. More recently it was observed that the progestins promegestone and medrogestone stimulate sulfotransferase for the formation of estrogen sulfates. Consequently, the action of progestins in blocking estradiol formation via sulfatase, or in stimulating the effect on sulfotransferase activity, can open interesting and new possibilities in clinical
applications in breast cancer.

Progestins and breast cancer.
Progestins exert their progestational activity by binding to the progesterone receptor (form A, the most active and form B, the less active) and may also interact with other steroid receptors (androgen, glucocorticoid, mineralocorticoid, estrogen). They can have important effects in other tissues besides the endometrium, including the breast, liver, bone and brain. The biological responses of progestins cover a very large domain: lipids, carbohydrates, proteins, water and electrolyte regulation, hemostasis, fibrinolysis, and cardiovascular and immunological systems. At present, more than 200 progestin compounds have been synthesized, but the biological response could be different from one to another depending on their structure, metabolism, receptor affinity, experimental conditions, target tissue or cell line, as well as the biological response considered. There is substantial evidence that mammary cancer tissue contains all the enzymes responsible for the local biosynthesis of estradiol (E(2)) from circulating precursors. Two principal pathways are implicated in the final steps of E(2) formation in breast cancer tissue: the 'aromatase pathway', which transforms androgens into estrogens, and the 'sulfatase pathway', which converts estrone sulfate (E(1)S) into estrone (E(1)) via estrone sulfatase. The final step is the conversion of weak E(1) to the potent biologically active E(2) via reductive 17beta-hydroxysteroid dehydrogenase type 1 activity. It is also well established that steroid sulfotransferases, which convert estrogens into their sulfates, are present in breast cancer tissues. It has been demonstrated that various progestins (e.g. nomegestrol acetate, medrogestone, promegestone) as well as tibolone and their metabolites can block the enzymes involved in E(2) bioformation (sulfatase, 17beta-hydroxysteroid dehydrogenase) in breast cancer cells. These substances can also stimulate the sulfotransferase activity which converts estrogens into the biologically inactive sulfates. The action of progestins in breast cancer is very controversial; some studies indicate an increase in breast cancer incidence, others show no difference and still others a significant decrease. Progestin action can also be a function of combination with other molecules (e.g. estrogens). In order to clarify and better understand the response of progestins in breast cancer (incidence, mortality), as well as in hormone replacement therapy or endocrine dysfunction, new clinical trials are needed studying other progestins as a function of the dose and period of treatment.

Treatment of estrogen-dependent gynecological disorders with the gonadotropin releasing hormone agonist buserelin.
The authors examined the effect and tolerability of buserelin in 40 women with endometriosis and ten women with uterine leiomyoma. Buserelin was given intranasally, 200 micrograms three times a day for 6 months. Laparoscopy was performed before and after, and ultrasonography during the treatment. Hormone and lipid profiles and other biochemical tests were run during the treatment. The bone mineral density was tested by dual photon absorptiometry before and after therapy in a group of patients. Although most of the patients complained of hot flushes, no women dropped out. AFS mean pelvic score decreased from 24.10 to 6.95 and the size of the fibroids decreased by 69% at the end of 6 months of treatment. In conclusion, our data suggest that the use of GnRH agonist has a place in the treatment of endometriosis and uterine leiomyoma but further studies are needed to conclude that buserelin given intranasally at a dose of 600 micrograms/day for 6 months is an alternative to other conventional medical treatment modalities in terms of pregnancy and recurrence rates.