Clinical uses of gonadotropin-releasing hormone analogues

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Gonadotropin-releasing hormone (Gn-RH) analogues are synthetic derivatives of the native hypothalamic peptide with alterations in their chemical structure that result in changes in biologic activity. Several Gn-RH agonists are available for clinical use, and all act through the same mechanism: first to stimulate and then to inhibit gonadotropin and gonadal steroid secretion by downregulating the pituitary Gn-RH receptors. This review should provide clinicians with a working knowledge of the physiologic and pharmacokinetic features of Gn-RH agonists. Although over 2000 articles concerning Gn-RH analogues have been published I chose to review only those that were the first to report a novel clinical application. Gn-RH agonists have proved to be extremely efficacious in treating gonadal steroid-dependent problems such as endometriosis, uterine leiomyoma, precocious puberty and prostate and breast cancers, and they have resulted in very few side effects. Long-term use may, however, lead to skeletal calcium loss in women as a consequence of hypoestrogenism. Further research is needed to prevent this and maintain clinical efficacy.

Les analogues de la gonadolibérine (Gn-RH) sont des dérivés synthétiques du peptide hypothalamique natif dont l'activité biologique a changé à la suite de modifications de leur structure chimique. Plusieurs agonistes de la Gn-RH sont disponibles pour usage clinique et tous agissent de la même façon : ils stimulent d'abord et inhibent ensuite la sécrétion de gonadotropine et de gonadostéroïdes en ralentissant les récepteurs hypophysaires de la Gn-RH. Cette revue devrait fournir aux cliniciens une connaissance pratique des caractéristiques physiologiques et pharmacocinétiques des agonistes de la Gn-RH. Même si l'on a publié plus de 2 000 articles sur les analogues de la gonadotropine, j'ai décidé de ne revoir que ceux qui ont été les premiers à faire état d'une nouvelle application clinique. Les agonistes de la Gn-RH se sont révélés extrêmement efficaces pour traiter des problèmes liés aux gonadostéroïdes comme l'endométriose, le léiomyome de l'utérus, la puberté précoce et le cancer du sein, et entraînent très peu d'effets secondaires. L'utilisation prolongée peut toutefois provoquer une déperdition de calcium squelettique chez les femmes à la suite d'hypoestrogénisme. Il faudra pousser les recherches pour prévenir cet effet secondaire et maintenir l'efficacité clinique des produits.

Gonadotropin-releasing hormone (Gn-RH) is a decapeptide hormone secreted by neurons with cell bodies in the mediobasal hypothalamus and is responsible for the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland. Since the sequencing of native Gn-RH in the late 1970s, synthetic derivatives (Gn-RH analogues) with agonistic or antagonistic biologic activity have been produced. This article should provide clinicians with a working knowledge of the physiologic and pharmacokinetic features of the potent Gn-RH agonists now available. Although several have been introduced to the Canadian market all are exactly the same in their mechanism of action and clinical effects. A MEDLINE search identified more than 2000 articles on Gn-RH ana-

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logues published from 1979 to 1989. However, I chose to review only the ones that were first to describe a novel clinical application along with a few supporting references.

At least two alterations in chemical structure serve to enhance the biologic activity of Gn-RH. These alterations include substitution of a D-amino acid for the glycine molecule at position 6 and deletion of the glycine molecule at position 10 and usually replacement by an *N*-ethylamide group.[1,2] These substitutions make the Gn-RH analogue resistant to degradation by circulating and tissue peptidases and increase its affinity for the Gn-RH receptor. In the case of Gn-RH agonists the result is biologic activity 60 to 150 times that of native Gn-RH. Fig. 1 shows the amino acid substitutions in the Gn-RH molecule that produce the Gn-RH agonist analogues available or soon to be available in Canada. No Gn-RH antagonist is yet available for clinical use, mainly because the early antagonists were not very potent and caused massive histamine release at the injection site. These problems are gradually being overcome, and it is likely that a new generation of Gn-RH antagonists will be available for clinical use soon. The rest of this review, however, will focus on Gn-RH agonists.

Pharmacodynamic features of Gn-RH agonists

After a single injection of a Gn-RH agonist, either subcutaneously or intravenously, there is a massive release of LH and FSH. Because the agonist is resistant to degradation a greater dose will not increase the peak LH and FSH response, although the duration of LH and FSH release is significantly prolonged.[3] A large dose of a Gn-RH agonist will result in the release of LH and FSH for 24 to 36 hours. Consequently repeated daily doses will produce a situation very similar to that of continuous Gn-RH infusion.

Downregulation of Gn-RH receptors

It was initially thought that Gn-RH agonists would be potent fertility-enhancing drugs because of their ability to release LH and FSH. However, in light of the experiments by Knobil,[4] which indicated that pulsatile release of LH and FSH every 60 to 90 minutes was necessary for follicular development, it soon became clear that Gn-RH agonist administration could not reproduce the physiologic state. Rather, after an initial stimulation there is a paradoxic inhibition of LH and FSH release that is now known to be due to Gn-RH receptor downregulation in the pituitary gland.

Gn-RH receptors, like all other peptide hormone ones, are cell surface receptors. Instead of adenosine 3′,5′-cyclic monophosphate, Gn-RH receptors use ionic calcium as a second messenger.[5] Normally a number of Gn-RH molecules travel in a pulse from the hypothalamus to the pituitary gland by way of the pituitary portal system and bind to Gn-RH receptors on the cell surface. LH and FSH are then released from the pituitary gland. The hormone-receptor complexes migrate to specialized areas of the cell surface called "coated pits," where they are internalized by a mechanism similar to pinocytosis.[6] Once inside the cell Gn-RH is degraded by peptidase, and it is thought that the receptors are recycled back to the cell surface for a subsequent pulse of Gn-RH. After Gn-RH agonist administration a similar recycling situation occurs, but because of the resistance of the Gn-RH agonist molecule to

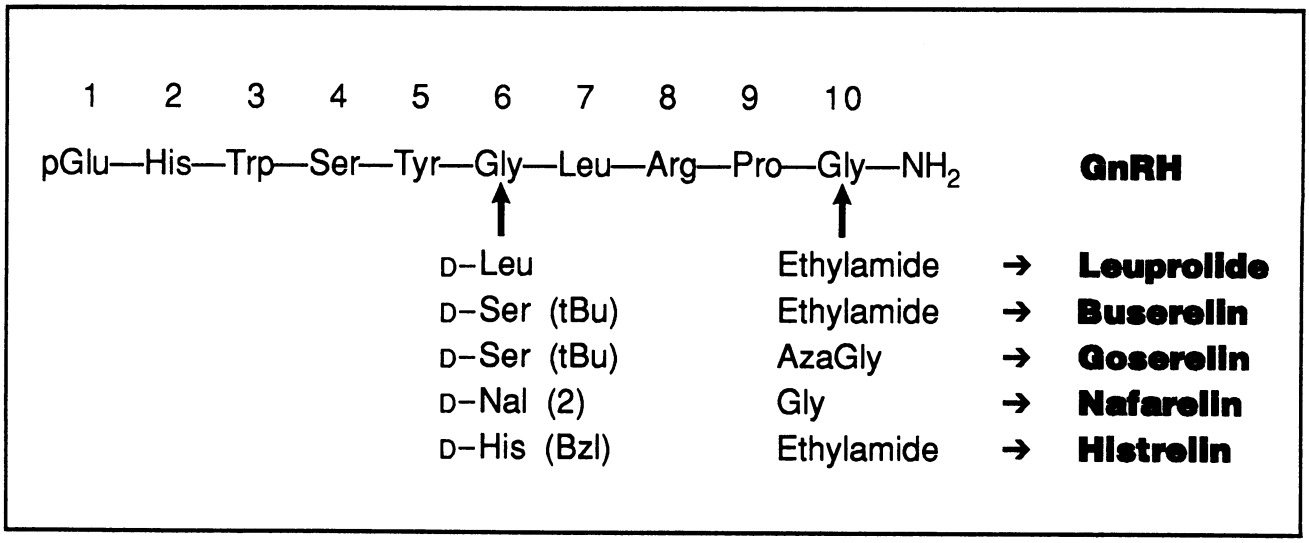

Fig. 1: Amino acid structure of gonadotropin-releasing hormone (Gn-RH) and substitutions that produce Gn-RH agonist analogues.

degradation by peptidase the recycling time is likely markedly prolonged. As a result, fewer and fewer Gn-RH receptors are present on the cell surface after subsequent injections of the agonist, and the gonadotrope becomes incapable of responding to endogenous Gn-RH or exogenous Gn-RH agonist stimulation with LH and FSH release. In the absence of LH and FSH stimulation the ovary ceases follicular development and estrogen production, and temporary menopause ensues. The term "medical castration" was coined by Meldrum and associates[7] to describe this paradoxic situation.

Clinical uses of Gn-RH agonists

Gn-RH agonists have widespread application in the treatment of conditions that necessitate a hypogonadal state. Conditions for which Gn-RH agonists are used to suppress ovarian estrogen production include endometriosis,[7] uterine leiomyoma,[8] precocious puberty,[9] premenstrual syndrome (PMS)[10] and breast cancer.[11] Gn-RH agonists have also been used to suppress ovarian androgen production in polycystic ovarian disease[12] and to prevent spontaneous LH surges during in-vitro fertilization.[13]

Similarly, Gn-RH agonist therapy may help to suppress testosterone production in males with such conditions as prostate cancer[14] and precocious puberty.[15]

Endometriosis

In 1980 it was suggested that the paradoxic antifertility effect of Gn-RH agonists might be useful in the treatment of endometriosis.[16] The first clinical paper to demonstrate such a use appeared in 1982.[7] Since then several studies have compared Gn-RH agonists with danazol, the standard drug used for endometriosis, and have shown them to be equally effective.[17] Thus, the choice between the two depends on acceptability, side effects and cost.

Uterine leiomyoma

Uterine leiomyomas are sensitive to estrogen. Filicori and collaborators[8] were the first to report that the size of uterine fibroids was reduced by Gn-RH agonist therapy, and a preliminary study by Maheux, Guilloteau and Lemay[18] demonstrated fibroid shrinkage in three patients with this therapy. Subsequently, reduction in uterine and fibroid size with Gn-RH agonist therapy for at least 3 months has been well documented.[19,20] Most fibroids return to pretreatment size within 6 to 9 months after therapy has been stopped. For perimenopausal women Gn-RH agonist treatment can serve as a temporary measure to stop fibroid-associated menorrhagia until occurrence of the natural menopause.

The most important use of Gn-RH agonists in the treatment of uterine leiomyoma is as an adjunct to surgery. Matta and colleagues[21] demonstrated a reduction in uterine blood flow and a significant difference in the amount of blood lost during myomectomy between patients treated for 3 months with a Gn-RH agonist and those given placebo.

Precocious puberty

The use of Gn-RH agonists to treat central precocious puberty was introduced in 1981.[9] Since then other studies have documented the efficacy of these agonists in inhibiting gonadotropin and gonadal steroid release in boys and girls.[15,22] Gn-RH agonist treatment is far superior to all previous therapies in that it stops menses, prevents the development of secondary sexual characteristics, permits the return of age-appropriate behaviour, slows somatic growth and bone maturation, and increases final adult height. Normal pubertal progression resumes after long-term Gn-RH agonist therapy is stopped, usually around the age of 11 years.[23]

PMS

PMS is characterized by the recurrence of psychologic, physical and behavioural symptoms in the luteal phase of the menstrual cycle. Its cause is not known, but there is no doubt that the condition is linked to the normal cyclic fluctuations of gonadal steroids. Muse and coworkers[10] demonstrated that suppression of ovarian function through long-term Gn-RH agonist therapy could result in the suppression of PMS symptoms. This therapy appears to be useful for confirming the diagnosis of PMS or for crisis management rather than as a long-term treatment because of the hypoestrogenism associated with it.

Prostate and breast cancers

Gn-RH agonist administration was shown by Redding and Schally[24] to reduce the growth of prostate tumours in rats. Clinically, the inhibition of pituitary gonadotropin release and the consequent suppression of testicular function have resulted in marked improvement in patients with late-stage prostate cancer.[14,25] This therapeutic approach has now replaced surgical castration.

In contrast, oophorectomy is still the standard treatment for metastatic breast cancer in premenopausal women. Response rates of about 33% and a median duration of remission of 10 to 14 months have been observed.[26] Animal studies dem-

onstrating a reduction of mammary tumour growth have led to clinical trials of Gn-RH agonists as adjunctive treatment for metastatic breast cancer in premenopausal and perimenopausal women.[11] Results appear to be equivalent to those of oophorectomy, and the physical and emotional trauma of permanent castration is avoided.[26] Although the reduction in tumour growth is thought to result from the suppression of gonadotropins and ovarian steroid production in-vitro studies have suggested a direct effect of Gn-RH agonists on tumour cells.[27,28]

Polycystic ovarian disease

Because of the selective effect of Gn-RH agonists on pituitary gonadotropes Chang and associates[12] were able to demonstrate that the excessive androgen production in patients with polycystic ovarian disease is ovarian in origin. Subsequent studies have confirmed that gonadotropin suppression with Gn-RH agonists inhibits ovarian androgen production in such patients without affecting adrenal steroid production.[29,30] Clinical improvement in oily skin, acne and hirsutism and reduction of ovarian size to normal has been observed in women with polycystic ovarian disease treated with long-term Gn-RH agonist therapy.[29,30] However, chronic anovulation and excessive androgen production recur after the cessation of treatment.[31]

In-vitro fertilization

Gn-RH agonists are widely used in in-vitro fertilization. They can suppress endogenous gonadotropin release in cases of tonic high LH levels and premature luteinization.[32] Also, Gn-RH agonists are frequently used to prevent spontaneous LH surges,[13] especially in programs that routinely cancel LH surge cycles because of scheduling problems. Finally, women who repeatedly exhibit suboptimal responses to attempted multiple follicular stimulation may respond better to endogenous gonadotropin suppression and controlled ovarian hyperstimulation through exogenous gonadotropin administration.[33]

Side effects

In general Gn-RH agonists are extremely safe since they have a selective action to downregulate Gn-RH receptors in the pituitary gland. As a result no other pituitary hormones are affected. Since Gn-RH agonists have no inherent steroidal activity their main side effects are a result of induced hypoestrogenism in women or hypoandrogenism in men. Because Gn-RH agonists are often used for 6 months or longer two major considerations are the potential for calcium loss from the skeleton and the possible adverse effects on lipid metabolism.

Calcium metabolism

The role of prolonged hypoestrogenism is well defined with respect to bone mineral loss. There appears to be a linear relation between the estrogen level and the rate of loss of bone mineral content.[34] In adults treated with Gn-RH agonists there may be loss of bone density because of induced hypoestrogenism or hypoandrogenism. Because women have a smaller skeletal mass they are likely at higher risk than men. Barnes, Mercer and Montner[35] and Dawood, Lewis and Ramos[36] have reported significant decreases in the mineral content of vertebrae after 6 months of Gn-RH agonist therapy. However, other investigators,[37,38] using well-designed clinical trials, have demonstrated no significant change in bone mass measured by dual photon absorptiometry.[37,38] In addition, it has been shown that bone mass lost during 6 months of Gn-RH agonist therapy may be rapidly replaced after the therapy is stopped. Although calcium intake is not likely a major factor in the prevention of osteoporosis in the absence of estrogen,[39] satisfactory intake of 1000 to 1500 mg of calcium daily is reasonable during the use of a Gn-RH agonist.

Among children with precocious puberty Comite and associates[22] found favourable effects of long-term Gn-RH agonist therapy on the growth rate, bone age advancement and predicted height. The long-term effects on their adult bone mineral content needs to be assessed over long periods. However, a negative impact seems unlikely since treatment occurs before puberty, when estrogen levels are normally very low.

Lipid metabolism

Valimaki and collaborators[40] recently compared the effects of a Gn-RH agonist with those of danazol on plasma lipid and lipoprotein levels in patients with endometriosis. This randomized clinical trial demonstrated that the plasma concentration of total high-density lipoprotein cholesterol (HDL-C) increased slightly in women given the Gn-RH agonist; however, there was no change in the total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels or in the apolipoprotein A-I and A-II levels. The findings of an elevated or unchanged HDL-C level have been confirmed by others.[17,41] In contrast, the women treated with danazol had profound decreases in the total HDL-C, HDL_2-C and apolipoprotein A-I levels and an increase of 25% in the LDL-C concentration. Therefore, despite the severe hypoestrogenism seen with Gn-RH agonist treatment no detri-

mental effect was observed on lipid metabolism. The fact that danazol had such a negative impact may be related to its androgenic steroidal activity.

Conclusion

Although only recently introduced, Gn-RH agonists have already proved useful in treating many conditions in which suppression of gonadal steroid activity is beneficial. These analogues are very safe, with a selective effect at the level of the pituitary gonadotrope and no demonstrable toxic effects. Recent developments such as depot forms of the agonists and the introduction of Gn-RH antagonists promise to extend the clinical applications of this exciting therapeutic modality. Since the effects of hypoestrogenism appear to be of major concern studies are needed to determine the effect of concomitant low-dose hormone replacement therapy on bone mineral content. Chronic conditions such as endometriosis and uterine leiomyoma may be suppressed through long-term Gn-RH agonist therapy supplemented by low-dose replacement therapy with estrogen or progestin, or both, to prevent hot flushes and to protect bone mass.

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Mar. 6-9, 1991: 2nd International Congress on the Immune Consequences of Trauma, Shock and Sepsis: Mechanisms and Therapeutic Approaches
Munich
Official language: English
Dr. Eugen Faist, local organizing secretary, Ludwig-Maximilians-universität Munich, Department of Surgery, Klinikum Großhadern, Postfach 70 12 60, 8000 Munich 70, Germany; telephone 011-49-89-70-95-34-41, FAX 011-49-89-70-95-7-00-44-18

Mar. 8, 1991: Psychiatric Disability: Facing the Challenge — Systems Development in Ontario: an Update
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Patricia Pettit or Carrie Clark, Clarke Institute of Psychiatry, 250 College St., Toronto, ON M5T 1R8; (416) 979-6852

Mar. 8-9, 1991: 1st European Congress on Ambulatory Surgery
Brussels Congress Centre
Official language: English (simultaneous interpretation into French and Dutch)
Administrative Secretariat, European Congress Consultants and Organizers, rue Vilain XIIII, 17a, B-1050, Brussels, Belgium; telephone 011-32-2-647-87-80, FAX 011-32-2-640-66-97

Mar. 8-9, 1991: Human Sexuality and Sex Therapy (sponsored by the Ontario Association for Marriage and Family Therapy in conjunction with the University of Western Ontario)
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Mar. 11-14, 1991: 1st Annual Northern Winter Symposium (sponsored by Dalhousie University with support from Laval University)
Chateau Mont-Sainte-Anne, Quebec
Tania Marchand, program coordinator, Division of Continuing Medical Education, Dalhousie University, Sir Charles Tupper Medical Building, Dalhousie University, Halifax, NS B3H 4H7; (902) 494-1596

Mar. 18-21, 1991: Cardiovascular Conference (sponsored by the American College of Cardiology, the Alberta Cardiovascular Society and the University of Alberta)
Chateau Lake Louise, Lake Louise, Alta.
Registration secretary, Extramural Programs, American College of Cardiology, 9111 Old Georgetown Rd., Bethesda, MD 20814; (301) 897-5400, ext. 226

Mar. 22, 1991: Psychiatric Disability: Facing the Challenge — Consumer Sensitization for Providers
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Mar. 22-24, 1991: 1st International Congress on Biological Response Modifiers (organized by the Inter-American Society for Chemotherapy [IASC])
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