Analogues of gonadotrophin releasing hormone

In 1960 McCann et al showed that a hypothalamic extract caused the release of luteinising hormone from the pituitary. Luteinising hormone releasing hormone (LHRH) was identified as a decapeptide in 1971 by Schally et al, and since the purified peptide was found to release both luteinising hormone and follicle stimulating hormone it was renamed gonadotrophin releasing hormone. Several analogues of gonadotrophin releasing hormone were synthesised in the hope of finding one with higher activity. These differed from the parent molecule by having amino acids substituted in varying positions, those analogues with substitutions at the sixth and 10th positions being described as “superactive” because a single injection led to supraphysiological increases in the pituitary gonadotrophins.

At first the superactive analogues were expected to be effective in inducing puberty in patients with hypogonadism. No such effect was observed, however; indeed, their repeated administration to animals actually resulted in a decrease in gonadotrophins and gonadal hormones with a regression of secondary sexual characteristics. This paradoxical effect of the long term administration of the “superactive” gonadotrophin releasing hormone analogues is explained because the normal mechanism depends on a response by the pituitary to the pulsatile release of endogenous gonadotrophin releasing hormone. The superactive analogues bind for prolonged periods to the pituitary receptors for gonadotrophin releasing hormone, rendering them unresponsive, so that after an initial stimulation the system becomes blocked with decreased secretion of the pituitary gonadotrophins and ultimately of the gonadal hormones. In addition, the superactive analogues may have a direct effect on the ovary and testis. Against initial expectations, the function of the superactive analogues, now renamed “long acting,” has turned out to be in conditions where gonadal activity needs to be suppressed rather than stimulated.

Initially long acting gonadotrophin releasing hormone analogues were investigated as possibly safer alternatives to contraceptives containing oestrogen. In Scandinavia Nilius, Bergquist, and Wide pioneered the assessment of d-Ser(Bu) LHRH ethylamide (buserelin) and succeeded in establishing an intranasal dosage regimen effective in suppressing ovulation in 24 of 26 women treated with between 400 and 600 μg daily. Linde et al then studied the antifertility effects in men of d-Trp6 Pro1 LHRH ethylamide, finding decreases in sperm counts in all eight of the subjects; in six the counts were lowered to below 6 × 10^6 sperms/ml. Although the men became impotent with treatment, depot testosterone supplements might overcome this side effect and allow the analogues to be used as male contraceptives.

In the late 1970s further applications of the long acting gonadotrophin releasing hormone analogues began to be recognised, and Crowley et al successfully treated a girl with idiopathic precocious puberty. Subsequently both girls and boys have been treated for this condition. With the long term use of these compounds, however, a relative resistance to treatment has been seen in girls but not in boys (C G D Brook, personal communication). The long acting analogues have been used in other conditions where gonadal “down regulation” is wanted, and in both endometriosis and idiopathic oedema (J A H Wass, personal communication) effective treatment has led to objective improvement. The d-Ser6 substituted analogue given intranasally has been used as an alternative treatment for severe acne.

Possibly the most important future application of this group of compounds is in the management of sex hormone dependent cancers. Their most obvious use is in prostatic cancer, the fourth most common tumour of men. This is known to be responsive to hormones, but no treatment has been shown to prolong survival. All current treatments have disadvantages, and some may actually affect survival adversely; thus conventional dosages of diethylstilboestrol result in an excess of deaths from cardiovascular causes. After the initial description in 1982 of the regression of canine prostatic cancer with Nac-p-Ci-D-Phe1,2 Trp3,4 Phe6,10 LHRH19 several reports appeared of the early results of the treatment of human carcinoma of the prostate. In these five studies 42 of 52 patients responded to treatment. We now need to know whether the analogues are as effective in the long term control of the disease as orchidectomy, and this point is being investigated in a randomised trial.

Klijn and de Jong reported the successful treatment with buserelin of two of four premenopausal patients with cancer of the breast. The advantages of the use of gonadotrophin releasing hormone analogues in premenopausal patients with breast cancer are not as apparent as in prostatic cancer. This is because the number of premenopausal women with breast cancer is limited and most patients prefer to undergo laparoscopic oophorectomy—so much so that a recent American trial of the arginine substituted analogue was not completed. The long acting analogues of gonadotrophin releasing hormone are, however, also being evaluated in postmenopausal women with breast cancer. If these compounds are confirmed to be effective further light might be cast on the mechanisms of response to hormones in breast cancer.

Long acting gonadotrophin releasing hormone analogues have not yet been investigated in other hormone related cancers but warrant investigation in patients with ovarian, endometrial, and possibly renal tumours. As well as being used in primary treatment the analogues may have a possible adjuvant function in preserving the fertility of young patients treated for curable cancers and lymphomas with sterilising cytotoxic chemotherapy. This possible use of the long acting analogues in Hodgkin’s disease is being investigated at St Bartholomew’s and the Christie Hospitals in a study that began in 1981.

Long acting gonadotrophin releasing hormone analogues have disadvantages in terms of ease of administration. These disadvantages are being overcome, and depot preparations are being developed by ICI and Hoechst. This class of compounds is of profound medical importance and the possible therapeutic
benefits of blocking analogues of other hypothalamic polypeptide hormones, such as growth hormone releasing factor and corticotropin releasing factor, are of enormous future interest.

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Patient information leaflets

Patients are increasingly eager for information about the drugs that they are prescribed, but does knowing about the side effects of drugs stop patients taking them? This is an important question for every physician who has to prescribe for his patients. Many prescribers think that information about unwanted side effects may frighten patients and put them off taking a useful medicine, but there is insufficient evidence to be sure that this is so. Television, radio, and newspapers devote increasing space to the subject of providing information for patients about drugs, usually on the principle that “bad news” describes several times the space that “good news” does. Unfortunately, there is no way of protecting a reader against misinformation or unbalanced views, and one result is an increasing preoccupation with “alternative medicine,” as illustrated by the recent onslaught from The Times on the medical profession.

The issue of patient information leaflets has been much debated in the United States, and the Food and Drug Administration has been considering whether it should be a requirement to issue such leaflets with all drugs obtained on prescription. The association of endometrial cancer with oestrogens led to a legal case in which the pharmaceutical industry and the doctors were in opposition to the Food and Drug Administration and the consumer groups, who supported a law requiring a leaflet with all tablets containing oestrogens. In the event the supporters won, but only in relation to this group of drugs. The law has now been extended, however, to cover intraterine contraceptive devices, isoproterenol, oestrogens, progesterons, and inhalers, but moves to apply it to all drugs have been halted.

Most studies have shown that providing written material helps patients to recall information. Looking at the content of a leaflet providing information for patients given benzodiazepines, Fisher and colleagues showed that with care it was possible to design a leaflet that met 85% of patients’ requirements. Traditionally the responsibility for informing the patient has rested with the prescribing physician, though there is evidence that he does not always have adequate pharmacological knowledge, is not always good at communication, and is often short of time. In these circumstances the provision of a carefully prepared leaflet, such as that described by Hermann and his colleagues, should help.

Controlled studies of patients suffering from hypertension or depression and those taking oral contraceptives, have shown that information leaflets increase patients’ knowledge of, and satisfaction with, their medication. George and his colleagues have confirmed this in patients in general practice receiving treatment with penicillin and non-steroidal anti-inflammatory drugs. They also suggest that compliance improved in those patients taking penicillin but decreased in those taking non-steroidal anti-inflammatory agents. Further confusing evidence comes from two studies in which the effect of information about the potential adverse effects of oestrogens convinced over half the patients that the risk was greater than the benefit, but only a small proportion of the patients failed to take the drug. Myers and Calvert looked at information related to amitriptyline and found that forewarning patients of side effects did not affect the incidence of reported effects or the rate at which medication was stopped unless the advice was written down, when more side effects were reported but fewer patients stopped treatment. Another study from general practice on patients with cystitis reported a gain in information by patients but no influence on their compliance.

As George