The Induction of Amenorrhoea

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SUMMARY: A survey has shown that many women favour eliminating menstruation and it has been suggested that therapeutic induction of amenorrhoea might be an advantage in female personnel mobilised for war. The traditional method has been to take the oral contraceptive pill continuously. This produces weight gain and other side-effects; spotting and breakthrough bleeding can be a problem initially. The method is however cheap. The Gonadotrophin Releasing Hormone (GnRH) analogue, goserelin, is extremely effective, produces less side-effects, but it is very expensive. Two synthetic steroids, danazol and gestrinone, are moderately effective, have a variety of prominent side-effects and are also quite expensive. With all these drugs normal menstruation resumes in the cycle after they are discontinued.

Although goserelin has many advantages over the continuously taken contraceptive pill, its cost precludes it from consideration as a means of eliminating menstruation.

Introduction

Demographic trends have brought into focus the increasing role of women in the Army (ROWITA). In war a number of gynaecological emergencies may therefore be anticipated. It is also suggested that there would be logistical advantages in making servicewomen amenorrhoeic following mobilisation, not least because of the decreased need for the provision of sanitary protection. The combined oestrogen/progestogen oral contraceptive pill, taken continuously, has been put forward as the method of choice.

The subject was highlighted on a recent Hospital exercise when a WRAC 'casualty', not realising the long duration of the exercise, brought insufficient sanitary protection and because the Hospital was not scaled for this item, she had to be withdrawn to her Unit.

There are a number of clinical conditions such as precocious puberty and endometriosis in which the therapeutic objective is to induce amenorrhoea. The aim of this paper is to review current methods of achieving this.

The over-riding consideration is that no coercion should be used to force servicewomen mobilised for war to accept therapeutic induction of amenorrhoea. Of course it is part of good medical management to discuss all the facts so that individuals can make an informed personal choice. This may not be a significant factor since in one study of the civilian population 80% favoured the concept of eliminating menstruation (1).

There are a number of questions that have to be asked of any therapy used for this purpose:

How effective is the drug?

What are the side-effects and would these affect fitness for role?

Are there long term complications?

Are menses restored immediately following cessation of therapy?

Are there likely to be problems with compliance?

What is the cost?

It is unlikely that the packaged drug would be bulky and thus replace one problem with another.

Physiology of Menstruation

In order to understand the mode of action of some of the drugs it is necessary to have an appreciation of the physiology of menstruation. This is shown schematically in Figure 1.

Oestrogen, principally 17 β -oestradiol, causes endometrial proliferation followed by shedding when steroid levels fall with luteolysis or follicular atresia. The corpus luteum also secretes progesterone which has

Fig 1. Hormones involved in the control of the menstrual cycle. (GnRH: gonadotrophin — releasing hormone; FSH: follicle — stimulating hormone; LH: luteinising hormone)

Fig 2. Plasma FSH and LH levels in samples taken every 15 minutes showing pulsatility of mainly LH secretion (c — o LH; o — o FSH).

synergistic effect with oestrogen in causing menstruation but is not capable itself of causing endometrial shedding. Oestrogen secretion itself is under the control of the pituitary gonadotrophins follicle stimulating hormone (FSH) and luteinising hormone (LH) which in turn are synthesised and released in response to gonadotrophin releasing hormone (GnRH). The latter is a hypothalamic deca-peptide which is thought to be secreted in pulses with a periodicity of 1 to 2 hours; hence the pulsatility of plasma LH and to a much lesser extent FSH levels (Fig 2). The cyclicity of menstruation is maintained by the positive and negative feed-back effects on the hypothalamic-pituitary axis.

It is thus theoretically possible to interrupt menstrual cycles by inhibiting production of GnRH, FSH and LH, or oestrogen or by inhibiting their effects on their target organs.

Production of Amenorrhoea

Continuous Oral Contraceptive Therapy.

The combined oestrogen/progestogen oral contraceptive pill acts by inhibiting gonadotrophin secretion but the pill itself also causes endometrial proliferation. However when the steroids are taken continuously the endometrium is not shed and amenorrhoea is induced. This method was favoured by Loudon *et al* (2) who used a tri-cycle pill regime with Minilyn (Organon) taken continuously for three months.

There were problems with breakthrough bleeding and spotting particularly if subjects missed tablets. These symptoms lessened in the third and fourth treatment cycles. Side-effects were weight gain of more than 2kg, breast tenderness, depression and headaches. These and other minor complications were responsible for a significant withdrawal rate. Nevertheless most subjects favoured the idea of less frequent periods. Minilyn con-

tains 0.05mg ethinylloestradiol and it is probable that the side-effects would be less with modern low dose pills. However this might be at the expense of poorer cycle control. Normal menses restarted during the pill-free interval.

The cost of twelve weeks therapy is less than £6 (3) and depending on the pill selected, most are less than £2.

Danazol.

Danazol is a synthetic derivative of ethisterone mainly used in the treatment of endometriosis. It is devoid of oestrogenic and progestational activity, but it possesses weak impeded androgenic properties. Its mode of action is incompletely understood, inhibition of gonadotrophin secretion (4) and anti-endometrial effects (5) both being claimed. On the maximum dose of 800mg daily in divided doses, only 75% of patients achieved amenorrhoea after one month although the success rate was better in those who started therapy on day one to five of the cycle and who were fully compliant (6). Smaller doses reduced the incidence of amenorrhoea although menstrual loss was less. Danazol in a daily dose of 100mg in our series of cyclic mastalgia patients did not induce amenorrhoea.

Side-effects are prominent on the more effective high dose regime and have been reviewed by Dmowski (7). As well as general effects which occur with many drugs there were those such as decrease in breast size, flushing, sweating and loss of libido specifically related to gonadotrophin inhibition, and acne, tendency to hirsutism, oedema, weight gain and voice change due to the androgenic action of the agent. Most of these side-effects had an incidence of less than 5% but acne was particularly prominent feature being present in 13.4% of the 704 patients reviewed in USA trials of the drug. On discontinuation of therapy there is a rebound of FSH and LH with ovulatory cycles re-appearing in a few weeks.

The drug is quite expensive and a twelve week course of the 800mg per day regime would cost almost £200 (3).

Gestrinone.

Gestrinone has recently been licensed in the UK for the treatment of endometriosis. It is a synthetic trienic 19-nor-steroid with antigonadotrophic, antiestrogenic and antiprogesterone effects. Like danazol it has weak androgenic properties. Coutinho (8) treated 20 patients with 5mg gestrinone orally twice weekly. Bleeding episodes during the first two months of treatment were rare and by the end of the second month all patients were amenorrhoeic.

The side-effects of gestrinone are similar to those of danazol; acne and seborrhoea developed in all subjects. Although the androgenic side-effects were eliminated by using a dosage of 2.5mg twice weekly, less than half the patients became amenorrhoeic on this regime (9). In the former study normal fertility was restored once therapy was withdrawn.

The drug is very expensive; a twelve week course would cost £450 (3).

GnRH Analogues.

As mentioned earlier there is very strong experimental evidence that GnRH is secreted in pulses which are reflected in the plasma FSH and LH levels. It also became apparent that continuous parenteral GnRH administration, although initially stimulating gonadotrophin production, produced a fall in FSH and LH secretion because of down-regulation of pituitary GnRH receptors. This in turn reduced gonadal activity. Continuous administration of the native deca-peptide is necessary to produce this effect because of its short half life. A number of potent analogues of GnRH have been produced in which the molecule has been manipulated so as to resist degradation (hence prolonging activity) and to enhance receptor binding (increase potency). Intermittent administration of these superagonists has been shown to mimic the gonadotrophin suppressing effect of continuous GnRH treatment. They have consequently found a therapeutic role in a number of conditions such as precocious puberty and carcinoma prostate where reduction in sex steroid secretion is beneficial.

There are two agents currently available in the UK, buserelin and goserelin. The latter is available in a depot dose of 3.6mg which is injected every 28 days. Buserelin on the other hand is administered sub-cutaneously or intra-nasally and has the disadvantage for the topic under discussion that multiple daily doses are required to achieve ovarian suppression. It is recommended in the pharmaceutical literature that goserelin is stored in a refrigerator but an informed source said this was unnecessary.

Goserelin given in the first day or two of the cycle subsequently induced amenorrhoea in all personally studied patients with cyclic mastalgia. In a series of six normal subjects half became amenorrhoeic while the remainder only had slight vaginal spotting (10). In our series patients were given the implant with the aid of local anaesthetic. The normal volunteers in the latter study found the injection simple and virtually painless without such assistance.

The main side-effect in both investigations cited above were pseudo-menopausal symptoms such as hot flushes which were induced by oestrogen withdrawal. However they were not regarded as severe and there were no defaulters in our six months study; treatment did of course relieve breast pain. One worry has been bone loss following the induced hypo-oestrogenism. This occurs but is reversible (11). Normal menstruation recurs around the anticipated eight weeks after discontinuing goserelin.

GnRH analogues are very expensive, a twelve week course of goserelin being just over £375 (3).

Future Developments.

There are a number of other agents currently being developed which potentially would inhibit menstruation.

Periods are not suppressed in the majority of patients taking the anti-oestrogen, tamoxifen. This is partly explained by it having some intrinsic oestrogenic activity. Search is currently being made for specific oestrogen antagonists. These would inhibit endometrial proliferation but since gonadotrophin secretion would be enhanced, ovarian hyper-stimulation might be an unacceptable complication.

As well as GnRH superagonists, analogues with GnRH antagonistic activity have been developed by means of amino acid substitution. Very few clinical trials have been conducted with this class of compounds but experimental work suggests they have to be administered in large doses with consequent high toxicity and cost.

Finally, the hormone inhibin which is naturally produced by the ovary and which blocks pituitary FSH secretion has been synthesised by genetic engineering both in the USA and Australia. It should not be long before the preparations are available for clinical trial.

Discussion

Postponement of menstruation by prolonging oral contraceptive therapy is often used for such social reasons as holidays and competitive sports. As already mentioned, some groups of women would welcome prolonged elimination of menses. Any drug therapy offered to servicewomen to achieve this aim would have to be effective, relatively free from side-effects and long term complications, cause no problem with compliance and be cheap. It is difficult to translate studies in patients to those in normal subjects since the former are likely to be more compliant and have a better sense of well-being as their symptoms are controlled.

Of the four drugs considered, the GnRH analogue goserelin was undoubtedly the most effective. Some of those taking continuous oral contraceptive therapy for three cycles initially suffered from spotting while danazol in particular did not always immediately produce amenorrhoea. It is an impression that the side-effects of goserelin were minimal but those on the 'placebo' fared no worse than those taking the oral contraceptive conventionally. Danazol and gestrinone were associated with prominent androgenic side-effects. None of the drugs caused long term problems and normal menses and, when desired, fertility occurred after the anticipated interval from stopping the drug. Subjects taking the oral contraceptive daily for three cycles missed tablets and this increased the incidence of spotting and break-through bleeding(2). Compliance might also be a problem with the multiple daily doses of danazol and may not necessarily be better with twice weekly gestrinone. On the other hand goserelin, since it is given monthly by the parenteral route, should not pose such a problem. However although so far the GnRH analogue seems the most attractive option, its expense would preclude its use. Danazol and gestrinone are the least

favoured. The cheapness of oral contraceptive therapy tips the balance strongly in supporting it as the method of choice.

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