Drug Treatment of Disease

THE OESTROGENS

BY

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The oestrogens available for clinical use fall into three main groups—namely, natural, synthetic, and semi-synthetic.

Natural Oestrogens.—Of these, oestradiol is the most potent and is administered in the form of esters (for example, benzoate or dipropionate) by intramuscular injection. The effect is relatively short-lived, and repeated injections—two or three times a week, or more often—are needed for sustained effects. The therapeutic dose is about 1 mg. Oestradiol valerianate is a long-acting ester, a single intramuscular injection of 10 mg. lasting for 20 to 30 days. Oestradiol benzoate microcrystals can also be used as a long-acting preparation for intramuscular injection.

Relative Potencies of Some Oral Oestrogens

Oestrogen	Potency Ratio	Approximate Equivalent Dose
Stilboestrol	1	1 mg.
Dienoestrol	0.26	4 mg.
Hexoestrol	0.05	20 mg.
Oestrone	0.04	25 mg.
Premarin	0.4	2.5 mg.
Methallenoestril	0.04	25 mg.
Ethinylloestradiol	25	0.05 mg.

Oestrone is weakly active by mouth, its potency (see Table) being approximately 1/25th that of stilboestrol. Oestrone sulphate is probably the principal ingredient of the mixture of "conjugated equine oestrogens" marketed under the name of "premarin." A 1.25-mg.

tablet of premarin is equivalent to about 0.5 mg. of stilboestrol. The great advantage of premarin is its remarkable freedom from toxic side-effects, in contrast to other oral oestrogens. Premarin has also been administered by intravenous injection.

Semi-synthetic Oestrogens.—In this group, ethinylloestradiol is the only important member, being the most potent of all oral oestrogens—about 25 times more active than stilboestrol. In doses of equivalent potency it is little if any less toxic than stilboestrol.

Synthetic Oestrogens.—Stilboestrol was the first synthetic oestrogen, having been produced 20 years ago by Sir Charles Dodds and his colleagues. It is still the most important because it is highly active and remarkably cheap—far cheaper than any other oestrogen preparation. It suffers from the serious drawback that in doses above 1 mg. a day it is likely to produce nausea, vomiting, abdominal discomfort, headache, and bloating in a proportion of patients varyingly estimated from 15 to 50%. Attempts to overcome this effect, such as by means of enteric coatings, have been unavailing.

Claims for reduced toxicity have been made for the related, more expensive, synthetic oestrogens dienioestrol and hexoestrol; but when their much inferior oestrogenic potency is taken into account (see Table) it becomes apparent that they are really no less toxic than stilboestrol.

Two other synthetic oestrogens, for which special properties have been claimed, are chlorotrianisene

("TACE") and methallenoestril ("vallestril"). The former is a long-acting pro-oestrogen—that is, it is not itself oestrogenic but is converted in the body (probably the liver) into an oestrogenically active metabolite. Its long duration is due to storage in the body fat, from which it is slowly released for subsequent activation. Because of this, it is difficult to compare it for activity with other oral oestrogens. Vallestril is a member of the allenolic acid series, and is only relatively weakly oestrogenic when given by mouth (potency about 1/25th that of stilboestrol). It is said to have little action on the endometrium, and so, in therapeutic doses, to be unlikely to cause uterine bleeding. Freedom from toxicity is also claimed, but, in evaluating this, its low potency has to be taken into consideration.

Replacement Therapy with Oestrogens

Like other hormones, oestrogens can be used for physiological or for pharmacological purposes. The former are replacement therapy in hypo-ovarian states, including the menopause. Indications for the latter are a miscellaneous group of conditions which will be considered in detail later.

Hypogonadism.—Delayed menarche as such requires no treatment, but difficulty arises in deciding when delayed menarche is really hypogonadism. Failure of sexual development by the age of, say, 17 justifies attention. If it is due to intrinsic ovarian insufficiency (primary hypogonadism), oestrogens are indicated to bring about and to maintain something approaching normal female development. If it is due to selective gonadotrophin insufficiency (secondary hypogonadism), oestrogen therapy is again worth a trial, and, if spontaneous menstruation does not occur, may have to be continued in order to maintain a semblance of normal female development.

The simplest treatment is to give oral oestrogens—for example, stilboestrol 2 mg. daily, in 20-day courses, repeating each course after 10 days or on the fifth day of the cycle if withdrawal bleeding occurs. Except in cases of primary hypogonadism, in which cyclic treatment must be continued, treatment should be interrupted after three or four cycles to see if spontaneous menstruation will occur.

An alternative method of treatment is to give a subcutaneous implant of oestradiol 50 mg., and, at monthly intervals for the next six months, either a single intramuscular injection of progesterone 50 mg. or a short course of oral progestagen. For the latter, ethisterone 60 mg. or norethisterone 15 mg. daily for three or four days will probably be effective.

The Menopause.—Many women experience no untoward climacteric symptoms. Others may have mild discomforts requiring no treatment or perhaps moderate sedation. But an appreciable minority suffer symptoms of real severity and deserve more specific therapy—namely, oestrogens. In addition, there is a small group of women of climacteric age who experience atypical symptoms, not clearly attributable to the menopause, for whom a trial of oestrogens is not unreasonable; a failure to respond indicates the non-climacteric origin of their symptoms.

There are three rules for the use of oestrogens at the climacteric: (1) The minimal effective dose should be prescribed. (2) The treatment should be in interrupted courses. (3) The dose should be diminished and treatment should be discontinued as soon as clinical response

permits. Based on these rules, the following general plan is usually quite effective.

Treatment is begun with stilboestrol 0.2 mg. daily, given for 28 days. If menstruation is still occurring, the course should be integrated with the periods and should be stopped if bleeding begins. Treatment should be omitted for 10 days to a fortnight. If the symptoms abate while the tablets are being taken, but reappear in full force when they are left off, the second course should remain at 0.2 mg. daily. However, if there has been little relapse while off treatment, the dose may be reduced to 0.1 mg. daily. If symptoms continue unabated, the dose may be increased up to 0.5 mg. or even 1 mg. daily, though with the latter—and rarely necessary—doses withdrawal bleeding may be expected and is obviously undesirable in a post-menopausal woman. It is not possible to say for how long cyclic treatment of this kind will have to be repeated—for a few months in some women, for a few years in others. The object, however, should always be to keep the dosage down as low as possible and to stop treatment as soon as possible.

"Difficult" patients may be encountered: these have nearly all been treated with excessively high dosage in the past, and relapse every time treatment is stopped; or they may have withdrawal bleedings even after moderate dosage. For some of these patients, combined oestrogen-androgen preparations ("climaton," "femadren," "mepilin," "miotrol," "mixogen," "primodian") may prove valuable, but it must be remembered that each tablet contains 2.5 to 4 mg. of methyltestosterone, and that even on one tablet a day some women may develop facial hirsuties. Treatment with combined tablets should follow the scheme outlined above. Methallenoestril may benefit the patient who tends to have withdrawal bleedings after stilboestrol or similar conventional oestrogens. A daily dose of 1 to 3 tablets of 3 mg. is recommended. Chlorotrianisene is claimed to be advantageous in that, following a single course of treatment with 2 capsules, each of 12 mg., daily for 30 or 60 days, 50% of patients do not require further treatment, while of the remainder relatively few will need more than one further similar course. My personal experience with this substance, while confirming its effectiveness, has failed to substantiate claims for its "once and for all" curative efficacy.

Objections to the use of oestrogen for the treatment of climacteric symptoms have been based on its carcinogenic potentialities. These have never been convincingly demonstrated in the human subject, and the risk may be regarded as minimal if the scheme of low-dosage interrupted therapy recommended is carried out. Continuous treatment might well be carcinogenic, and in any case can be expected to produce prolonged and irregular uterine bleeding which may be difficult to control. All post-menopausal women who develop uterine bleeding must be subjected to proper diagnostic investigation.

Pharmacological Uses of Oestrogens

Oestrogens have been employed pharmacologically for a great many purposes, to most of which only brief reference will be possible here.

Menstrual Irregularities.—This condition is probably the commonest in which oestrogens are prescribed for their pharmacological effect. For secondary amenorrhoea and for oligomenorrhoea, cyclic oestrogen therapy at a dose of about 2 mg. daily of stilboestrol

(or the equivalent of other oestrogens) will usually provoke regular withdrawal bleedings, though it is relatively uncommon for cessation of treatment to be followed by regular spontaneous menstruation. Prolonged and irregular bleeding of dysfunctional type (which must first be proved by appropriate investigations) may be controlled by similar oestrogen therapy in many, though not all, cases. If bleeding is not arrested within 48 hours, the oestrogen dose should be doubled and maintained at that level for the rest of the 20-day course. If bleeding starts again before the course is completed, treatment should be stopped and resumed again five days later. After a regular menstrual cycle has been established, the oestrogen may be combined with an oral progestogen, given during the second half of the oestrogen course in the hope that this may lead to the occurrence of ovulation. Considerations of space preclude a more detailed exposition of the methods of treating dysfunctional uterine bleeding.

Dysmenorrhoea.—In the absence of pelvic disease this usually occurs only in ovular cycles, and the inhibition of ovulation by means of 20-day courses of oestrogen, beginning on the second or third day of the cycle, produces painless withdrawal bleedings. If such withdrawal bleedings are still painful, a wholly psychogenic basis for the dysmenorrhoea must be considered. In order to avoid the potential risks of prolonged inhibition of ovulation, it seems wise never to give more than three successive courses of treatment. The patient is then told to wait until she has another painful period, when a further three courses of treatment can be given, and so on. The dose used should be the lowest that will regularly inhibit ovulation: it varies from patient to patient, but is usually about 1.5–2 mg. of stilboestrol daily.

An alternative method, intended to obviate the drawback of inhibiting ovulation, is to administer a post-ovular course of oestrogen, such as dienestrol 10–15 mg. daily from the 15th cycle day for 10 days. There is no obvious rationale to this method, which, in the writer's experience, has only occasionally been an effective treatment for dysmenorrhoea.

Vaginitis.—In senile vaginitis, oestrogen-containing pessaries are the most convenient means of obtaining a local oestrogenic effect without the undesirable systemic actions. A pessary containing 0.1 to 0.5 mg. of stilboestrol is suitable, and may also be used for pre-pubertal vulvo-vaginitis. If, in small girls, insertion of the pessary proves difficult, the oestrogen may be applied locally as an ointment.

Suppression of Lactation.—It is now generally agreed that oestrogens do not inhibit lactation, but merely prevent the engorgement which follows cessation of suckling, itself the true cause of inhibition of lactation. Widely differing regimes have been successfully employed. In the Obstetric Unit at University College Hospital the standard dosage schedule is as follows: stilboestrol 5 mg. three times a day for three days, twice a day for three days, daily for three days, 1 mg. three times a day for three days, twice a day for three days, daily for three days. Good results have been reported with chlorotrianisene in an average dose of 4 capsules daily for seven days.

Palliation of Hormone-dependent Carcinomata.—The oestrogen treatment of carcinoma of the prostate was first introduced by Huggins 16 years ago. Stilboestrol has been most widely used, and high dosage—perhaps

excessively high—has been the rule. Since this treatment produces physiological castration, there seems to be no valid reason for employing surgical castration as well, though this is often done. The treatment is usually surprisingly well tolerated, though gynaecomastia, often painful, is an unavoidable side-effect.

In similar fashion oestrogens have been used for the palliation of inoperable carcinoma of the breast. They are most likely to be of value in post-menopausal women, but, as with other attempts at altering the endocrine environment, it is not possible to predict which patients will and which will not respond.

Miscellaneous Conditions.—In certain collagen diseases (for example, lupus erythematosus disseminatus, rheumatoid arthritis), at about the time of the climacteric the cyclic administration of small doses of oestrogen may lower the maintenance dose of corticosteroid remarkably, and so permit good control without the risk of side-effects.

In coronary thrombosis the use of oestrogens has been advocated because they lower the plasma cholesterol; clearly, the feminizing effects are a serious disadvantage. This objection is also true for the oestrogen treatment of severe acne in adolescent males, but it is less valid for the use of oestrogens in the treatment of uncontrollable sex urges. The individuals concerned here have mostly been homosexuals whose activities have brought them into conflict with the law, and who have felt unable to resist the temptation to further similar activities. Comparatively small doses, such as 1 or 2 mg. of stilboestrol daily, may suffice to damp down the sex urge to a level which no longer jeopardizes the patient's freedom, though the fundamental deviation of sexual outlook remains. It may be agreed that the testicular atrophy and gynaecomastia which must accompany effective oestrogen therapy are not too high a price for these unfortunate individuals to pay.

OPERATIONAL RESEARCH IN THE UNIVERSITY*

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In this paper I am hoping to interest colleagues concerned with medical education in what has been called "operational research," the study of what goes on, of what happens to the student, and reciprocally to his university environment, as the two go through their course together. This is something different from the selection research with which many readers will already be familiar.

In the university some are becoming very doubtful of the value of selection research; or, at any rate, of selection research unaccompanied by operational research. As illustration, let us consider the standards expected in first-year examinations. It has been suggested that each faculty and department has its own unconsciously held norm of a proper casualty rate for the end of the first year, departure from which is regarded with discomfort. (The pass-rate differences

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