SHORT REPORTS

The natural oestrogenic hormone oestradiol as a new component of combined oral contraceptives

Thromboembolism is a rare but serious side effect of combined oral contraceptive use. Åstedt *et al*¹ showed a defect in the fibrinolytic system in women who had had deep vein thrombosis when using combined oral contraceptives, especially in the fibrinolytic activator content in the vessel walls, which activates this defence system against thrombosis. The synthetic oestrogenic compound ethinylloestradiol depresses the activator content of the vessel walls.² Biologically equivalent doses of the natural oestrogenic hormone oestradiol, however, do not have this effect.³ Oestradiol impairs liver function less than synthetic oestrogens⁴ and might therefore be a safer component of oral contraceptives.⁵

We undertook a pilot study of the side effects of an oral contraceptive pill containing oestradiol and norethisterone to find out whether natural oestrogen might be useful in the development of a new pill.

Subjects, methods, and results

The pill contained 4 mg of micronised oestradiol and 3 mg norethisterone (Netagen; Novo Pharmaceuticals, Denmark). It was taken for 21 days and then withdrawn for seven days of consecutive cycles. The study was approved by the Swedish Medical and Social Welfare Board. Volunteers were 25 normally menstruating, apparently healthy women of whom 17 had never used combined oral contraceptives before, five had previously used them, and three had been taking pure gestagenic preparations. The study lasted for one year, during which time the women were asked to note bleeding abnormalities, amenorrhoea, dysmenorrhoea, premenstrual tension, nausea, and emotional disturbances. Weight gain of more than 2 kg and an increase in systolic or diastolic blood pressure of more than 10 mm Hg were recorded.

No pregnancies or thromboembolic incidents occurred during the study (204 cycles). Spotting occurred in seven women, mainly during the first cycle, and never after the third. Two women developed amenorrhoea, one of whom had previously had amenorrhoea before and during the use of conventional combined oral contraceptives. Two women had dysmenorrhoea, but had had similar pain before they used the pill. Emotional disturbances were noted by two. Premenstrual tension or nausea did not occur. The menstrual flow was described as unchanged by 12 and decreased by the remaining 13. Body weight increased (> 2 kg) in four, remained unchanged in 19, and decreased in two. No increase in blood pressure was recorded.

Eleven of the women stopped taking the pill after 3-6 months, five because of desired pregnancy, two because of amenorrhoea, one because of spotting, one because of continued dysmenorrhoea, and two because of emotional disturbances. Fourteen women continued taking Netagen, were satisfied, and felt well.

Comment

Oestradiol is a natural oestrogen obtained from soya beans. It has hitherto proved unsuitable for use in combined oral contraceptives as it is not readily absorbed. This problem has, however, been resolved by the new micronising technique.

Although six of the 25 volunteers stopped taking Netagen because of side effects, five of them had had similar complaints when using conventional combined oral contraceptives or no pill at all. Only one of the cases of amenorrhoea could be ascribed to Netagen. It should also be pointed out that eight of the 25 women were using or had used various combined oral contraceptives or pure gestagenic pills before the trial, and most of these wanted to try the new pill because of side effects associated with these preparations.

The amounts and balance of oestradiol and norethisterone in the Netagen were probably not ideal and may require adjustment. But since oestradiol seems less likely to cause thromboembolic complications, the results of this pilot study suggest that it may be useful as a new component of combined oral contraceptives.

³ Åstedt, B. and Jeppsson, S., *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1974, **81**, 719.

⁴ Jeppsson, S. and Rannevik, G., *British Journal of Obstetrics and Gynaecology*, 1976, **83**, 567.

⁵ Åstedt, B., *American Heart Journal*, 1975, **90**, 1.

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Anterior tibial compartment syndrome associated with alcohol abuse

The anterior tibial compartment syndrome is a rare condition characterised by severe pain over the anterolateral aspect of the calves followed by footdrop. Histologically there is ischaemic necrosis of the anterior tibial muscles. There are many predisposing factors, of which exercise is the commonest.^{1,2}

We report a case associated with alcohol abuse. Although acute in onset, the condition was painless owing to a coexistent peripheral neuropathy.

Case report

A 55-year-old man presented with a 30-hour history of progressive difficulty in walking culminating in a fall from which he was unable to rise. He had noticed tingling in his feet but no pain. For 35 years he had drunk 10 pints (5.7 l) of beer and half a bottle of sherry daily. There had been a gradual increase in his consumption before admission but no recent "binge." He was taking lithium carbonate for a manic depressive illness.

On examination he looked unwell and his temperature was 38°C. The anterolateral aspects of both calves were red, warm, and tense, though not tender. Neurological abnormalities were confined to the legs and consisted of moderate weakness of hip flexion and absent dorsiflexion at both ankles; deep pain was absent, and touch, pin-prick, and temperature appreciation were reduced below the knees; vibration and position sense were diminished in the toes; ankle jerks were absent.

Haemoglobin was 15.2 g/dl, erythrocyte sedimentation rate 38 mm in the first hour (Westergren), fasting pyruvate 100 µmol/l (0.9 mg/100 ml) (normal 45-80 µmol/l; 0.4-0.7 mg/100 ml), and creatine phosphokinase 2250 U/l (normal up to 80 U/l). Serum lithium was within the therapeutic range. Electromyography showed polyphasic units of short and long duration in the right gastrocnemius, quadriceps, and tibialis anterior; motor nerve conduction velocities were normal; and ulnar and median sensory nerve action potentials were reduced in amplitude. Biopsy of extensor hallucis longus showed infarcted muscle.

After alcohol withdrawal and treatment with Parentrovite his neuropathy improved, and two weeks later the only abnormalities were bilateral footdrop and impaired deep pain sensation below the knees. Creatine phosphokinase had fallen to 270 U/l and the fasting pyruvate was within normal limits. Two months later the footdrop was unchanged.

Comment

This case is unusual for two reasons. Firstly, alcohol abuse seems to have been the cause of the anterior tibial compartment syndrome, and this has not previously been reported. Certainly none of the known causes of the syndrome were present, and it seems unlikely

¹ Åstedt, B. *et al*, *British Medical Journal*, 1973, **4**, 631.

² Åstedt, B., *Acta Obstetrica et Gynecologica Scandinavica*, 1971, **50**, 279.