Cyclofenil as a possible cause of non-arteritic anterior ischaemic optic neuropathy

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SUMMARY

A 27-year-old woman receiving the steroid drug cyclofenil as a fertility adjunct, experienced blurred vision 24 h after missing a dose and taking a double dose to 'catch up' with her therapeutic protocol. She was found to have a non-arteritic anterior ischaemic optic neuropathy with a visual hemifield defect and impaired optic nerve function, which has not since shown any recovery. This case highlights the prothrombotic potential for the drug when used above normal dosing range, and is therefore of great guidance for those initiating it as a fertility treatment, or in unlicensed use.

BACKGROUND

Cyclofenil is not a first-line fertility drug, and as such there is very little information on adverse effects and dose-related consequences available for clinicians who choose to use it. This case highlights the prothrombotic potential for the drug when used above normal dosing range, and is therefore of great guidance for those initiating it as a fertility treatment.

There are no data available on current rates of usage; however, the Medicines and Healthcare Products Regulatory Authority (MHRA) lists 104 events linked to cyclofenil since 1963, with 67 being classified as adverse drug events and 1 listed as fatal, which is related to ovarian cancer.¹ Anecdotal evidence suggests trends for unlicensed use as a body building aid. The International Federation of Body Building and fitness (IFBB) lists cyclofenil as a banned substance.²

CASE PRESENTATION

A 27-year-old woman was started on cyclofenil as a fertility treatment with a standard dosing protocol of 200 mg three times daily, orally. After missing an

evening dose, she was advised by her fertility centre to take a double dose of 400 mg the following day. The rationale behind this was that the treatment course was to induce ovarian stimulation, so hormonal levels were required to be maintained at a constant level. Unfortunately, she experienced blurred vision in her right eye 24 h later. She presented to eye casualty, where she was found to have reduced vision of 6/12 the right eye, a relative afferent papillary defect and swollen optic disc superiorly. She was diagnosed with a non-arteritic anterior ischaemic optic neuropathy (NAION). Her medical history was clear, with no personal or family history of thrombosis and no history of smoking. She had no history of migraine, and was on no other hormonal preparations. Her obstetric history did not include miscarriage and she was on no other regular medications. She had neither been identified with hypertension or diabetes at time, nor has been since. She had no arrhythmias and no carotid bruit. She had no air travel history, no periods of immobility preceding the event and had never smoked tobacco.

INVESTIGATIONS

Goldman visual field testing revealed a right-sided inferior altitudinal hemifield defect while left visual field was normal (figure 1). Ishihara colour vision cards revealed reduced colour perception in the right eye.

Medical examination, imaging of the brain and orbits, carotid doppler as well as extensive haematological and biochemical investigations were performed but there was no abnormality.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis included optic disc compression, diabetic papillopathy, syphilitic or

Figure 1 Goldman visual fields: right-sided inferior altitudinal hemifield defect.

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Figure 2 Fundus photos 1 year later: pale superotemporal segment of the right optic disc.

sarcoid-associated optic neuritis but there was no positive finding to suggest any of these conditions so the diagnosis of NAION was made.

OUTCOME AND FOLLOW-UP

No proven effective therapy for NAION exists. Five years later, the visual field defect persists and on funduscopy there is a pale superior segment on the right optic disc (figure 2) which corresponds with the field defect. The patient's general practitioner reported the adverse event to the MHRA soon after its occurrence.

DISCUSSION

Cyclofenil is a selective oestrogen receptor modulator (SERM), which was postulated as a treatment for infertility, and also for Raynaud's phenomenon occurring in patients with scleroderma. Several case reports of empirical use in both indications emerged in the 1980s; however, a more recent Cochrane review³ showed insufficient evidence for use in scleroderma. In fertility, however, it has been more successful, with a report from Japan⁴ showing at least equal rates of efficacy compared to the more mainstream fertility drug, clomiphene. There are at least five reports^{5–8} of a reversible hepatitis induced by cyclofenil during treatment cycles, which have also served to put its use out of vogue in recent years, and thus it has largely been superseded by clomiphene in fertility use.

In this case, an increased dose of cyclofenil was the only identifiable risk factor for an otherwise rare condition among this age group. ION is a potentially debilitating event, and particularly so in this younger age-group where driving and ability to work may be affected by visual field defects.

The pathogenesis of NAION, in general, is currently unclear, but is widely agreed to be due to a compartment syndrome in the nerve fibres at the optic nerve head, arising from a microvascular ischaemic event. Current theories include the role of prothrombotic states and impaired autoregulation of the vascular endothelium at the nerve head.⁹ These factors may both be influenced by oestrogen receptor control.

While previous reports have linked oestrogen-containing oral contraceptives¹⁰ and other SERM compounds such as tamoxifen and raloxifen¹¹ to thrombotic disease, we have found no previous reports on cyclofenil causing similar effects. The exact mechanism of thrombotic disease in patients on SERMs is unidentified as of yet. Cano *et al*¹² reviewed the literature concerning SERMs and associated incidence of coronary heart disease in 2007, and found evidence for protection against atherosclerosis formation, although thrombosis risk was increased. More recently, Artero *et al*¹³ discussed the balance between

vascular endothelial regulation and promotion of platelet aggregation, both of which are known to be effects of SERMs. Shah *et al*¹⁴ recently demonstrated that another SERM, tamoxifen, raises platelet intracellular calcium ions, and so may be responsible for promoting platelet aggregation.

Given the current uncertainty surrounding pathogenesis of SERM-related thrombosis, and the case outlined above, we would urge caution when considering cyclofenil as an adjunct in fertility treatment or otherwise, and particularly to consider risk factors for occlusive disease before starting its use.

Learning points

- ▶ Cyclofenil is a steroid compound selective oestrogen receptor molecule used as a fertility adjunct.
- ▶ Care should be taken to discuss risks and risk factors when initiating the treatment to avoid similar vascular occlusive events. Those considering unlicensed use should be urged to consult with their general practitioner to discuss risk factors.
- ▶ Cyclofenil should be avoided in those with history of migraine, as with oestrogen-containing oral contraceptives, due to occlusive potential.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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