Safer prescribing of therapeutic norethisterone for women at risk of venous thromboembolism

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Background

More than 794 000 prescriptions are written for therapeutic (as opposed to contraceptive) use of norethisterone (or its synonym norethindrone) in the UK each year (data on file, Bayer plc). Although its licensed indications include "metropathia haemorrhagica, premenstrual syndrome, postponement of menstruation, endometriosis, menorrhagia and dysmenorrhea"[1] most clinicians prescribe it to stop an episode of heavy menstrual bleeding or use it 'off-label' to help regulate irregular bleeding associated with hormonal contraception such as progestogen-only implants or injectables.[2] In these situations, the dose prescribed is generally 10–20 mg per day, compared to the 0.5–1 mg per day in contraceptive formulations. Some have called therapeutic norethisterone a 'lifestyle' drug as its seasonal prescribing peaks during the UK summer months suggest an increased use solely for delaying menstruation during holidays.[3]

Adverse effects

High-dose (therapeutic) norethisterone was thought to be free of serious adverse effects. Doubts, however, first started to emerge in 1999 when two studies[4 5] reported an increased incidence of venous thromboembolism (VTE) in women taking high-dose oral progestogens for therapeutic indications. No particular progestogen was named but the authors cautioned against prescribing 'therapeutic' doses in women at increased risk of VTE. They suggested that either the progestogen increased VTE risk or women requiring therapeutic doses of progestogens may have an inherent increased VTE risk. More recently Sundstrom *et al.* proposed that "menorrhagia could be a prothrombotic condition" when their nested, case-control study performed using the UK General Practice Research Database found that tranexamic acid, mefenamic acid and high-dose norethisterone were associated with an increased risk of VTE.[6]

Metabolic aspects

Back in the 1990s, preliminary studies reported that a small percentage of norethisterone and its ester norethisterone acetate (NETA) could be aromatised to ethinylestradiol (EE).[7 8] It was postulated that this low rate of aromatisation varied from individual to individual and its effects were likely to be negligible in postmenopausal women taking estradiol in hormone replacement preparations containing norethisterone although, interestingly, these products resulted in increased bone mineral density when compared to estradiol-alone therapies.[8 9]

In 1997, Kuhnz *et al.* generated data showing that norethisterone was partly metabolised to EE after oral administration of norethisterone or NETA in humans.[10] They concluded that this conversion resulted in a dose that was equivalent to taking 4–6 μg EE for every 1 mg oral norethisterone/NETA ingested. Although these data were derived from a study in postmenopausal women, it was felt that the study results could be extrapolated to premenopausal women.

Further research estimated the conversion ratio of NETA to EE to be between 0.2% and 0.33% for different doses.[11] This is of no relevance when these progestogens are taken in low-dose progestogen-only pills or combined oral contraceptive pills (COCs)[12] but Chu *et al.* concluded that a daily dose of 10–20 mg NETA equates to taking a 20–30 μg EE COC[11] and probably explains why high-dose norethisterone and its ester are effective at delaying and regulating menstrual bleeding. From available evidence the structural peculiarity of norethisterone, the norethisterone prodrug norethynodrel, and perhaps one of the metabolites of tibolone means that they are readily aromatised by cytochrome P450 mono-oxygenases in the adult liver to EE.[13] There are no implications for other progestogens in either low or high doses, since these structural issues do not apply.[13–15]

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Safety information

Based on the data of Kuhnz *et al*.[10] Bayer plc (the manufacturer of Primolut N®, a brand product containing norethisterone 5 mg), have decided to update the reference safety information in order to point out that 1 mg orally administered norethisterone/NETA metabolises to 4–6 μg EE.[10] This is also valid for all generic norethisterone preparations manufactured and distributed by other worldwide pharmaceutical companies.

Therapeutic doses of norethisterone should now be seen as a combination-like product with estrogenic and progestogenic properties. Considering the known data for COCs, Bayer plc has adapted the reference safety information for Primolut N to provide similar 'contraindications' and 'warnings and precautions' sections as EE-containing COCs. Approval is currently being sought with the UK Medicines and Healthcare products Regulatory Authority to include these labelling changes in Primolut N's Summary of Product Characteristics.

This change in labelling should lead to safer prescribing of progestogens for women with dysfunctional uterine bleeding. Based on currently available data the updated reference safety information does not change the overall positive benefit/risk balance for prescribing therapeutic doses of norethisterone in those at low risk of VTE. However, health care professionals will need to reassess the need for such treatment in women at high risk of VTE. One very small study has suggested that 10 mg medroxyprogesterone acetate, administered three times a day, is as effective in reducing heavy menstrual bleeding as a daily dose of 15 mg norethisterone taken from Day 12 to Day 25.[16] Therefore, where clinical indications remain in those who are obese, immobile, about to undergo surgery, carriers of a thrombophilia or have a personal or strong family history of VTE, medroxyprogesterone acetate is a suitable alternative.

Competing interests Dr Mansour declares no support from any organisation for the submitted work. Dr Mansour has received research grants and honoraria for attending advisory board meetings, developing and delivering educational presentations from Astellas, Bayer plc, Consilient Healthcare, HRA Pharma and MSD. Dr Mansour declares that there are no other relationships or activities that could appear to have influenced the submitted work.

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