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Implications of the Pharmacovigilance Risk Assessment Committee recommendations for the treatment of genitourinary syndrome

The European Medicines Agency's Pharmacovigilance Risk Assessment Committee has issued statements regarding limiting the use of high-dose oestradiol creams by women experiencing the genitourinary syndrome of menopause, and such statements carry much medicolegal weight. Although a low dose is most often used, some clinicians opt to use higher dose creams with close monitoring of the patient. The committee should publish the evidence behind these statements or amend its official position.

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The menopause is a time of change. Although for people in the Western world, it is often heralded with at least some degree of trepidation, in other societies the menopause, for a number of reasons, is gladly anticipated. This editorial looks at the management of those women who experience sufficient discomfort during the menopause to require medical treatment, including local hormone replacement.

Menopausal symptoms

The menopause leads to many different changes, which occur to a varying degree in individual women. While osteoporosis may predominate in one patient, atrophic genitourinary changes may be the most prominent symptom in another. While symptoms such as vasomotor instability may respond to the smallest doses of oestrogen, oestrogen deprivation atrophy may make the genitourinary syndrome of menopause a great clinical challenge. Not only are long durations of oestrogen treatment required, but much individual psychological support is often needed. Such support depends on the personality of the patient as well as other challenges they face, which may vary with family conditions, occupation and other factors.

Genitourinary syndrome of menopause, including the cysto-urethral syndrome, may be simply referred to as vulvo-vaginal atrophy, which may or may not be symptomatic. Although such atrophy is universal, its extent and rate of development differs between individuals and the severity of symptoms may not necessarily be related to the degree of atrophy. Symptoms include increased frequency of micturition, nocturia, dysuria, a sense of incomplete voiding, dyspareunia, repeated and frequent episodes of cystitis (true or pseudo) and dysfunctional incontinence. While coital problems may be dealt with by sexual abstinence, the urinary symptoms may significantly disrupt life and daily activities. Hormone replacement therapy in the form of local vaginal oestrogen may help ameliorate the atrophy, but the place of oral oestrogen remains unconfirmed (Raz, 2011). Vaginal oestrogen reduces the incidence of urinary tract infections in this group (Perrotta et al, 2008). Response to such treatment may vary but months of treatment and review may be necessary before the patient obtains significant relief.

With this in mind, it was surprising that, in a press release dated 17 January 2020, the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency reconfirmed its recommendation limiting the use of high-strength oestradiol creams containing 100 micrograms/g (0.01%) to a single treatment period of up to 4 weeks (European Medicines Agency, 2020). Furthermore, the size of tube has also been specifically limited to 25 g. A number of specific products are targeted, including Linoladiol, Linoladiol N, Linoladiol Oestradiol, Oestradiol Wolff and Montadiol. This statement confirmed the Pharmacovigilance Risk Assessment Committee's original 2014 review and decision. The latest Pharmacovigilance Risk Assessment Committee (European Medicines Agency, 2020)

Key points

- The genitourinary syndrome is a significant symptom of menopause which requires specific treatment.
- The European Pharmacovigilance Risk Assessment Committee has published recommendations warning against the use of higher dose oestradiol creams which may be required to manage this condition.
- There are transatlantic differences in opinions regarding the treatment of genitourinary syndrome.
- The Pharmacovigilance Risk Assessment Committee could offer better clinical guidance if it published the data analysed to reach its conclusions.

review elicited a very reasonably expressed response from the North American Menopause Society (Faubion, 2019). Among other salient points, the North American Menopause Society pointed out the lack of evidence-based arguments used by Pharmacovigilance Risk Assessment Committee. Furthermore, it stressed that the genitourinary syndrome of menopause is a chronic and progressive condition which can devastate a woman's health and quality of life, and does not resolve spontaneously with time or short-term treatment.

In the UK, gynaecologists use vaginal creams containing an upper limit of 10 micrograms following the British Menopause Society guidance (Pitkin, 2018). This is based on the fact that the serum level of oestrogen does not rise above the normal range of the pre-menopausal woman when a low dose of oestrogen cream is used. However, this does not diminish the value of the 2019 North American Menopause Society response (Faubion, 2019). The Pharmacovigilance Risk Assessment Committee seems to be failing to recognise the need for individual use of higher dose oestrogen cream, well monitored by experienced gynaecologists.

It is also important to be aware of the medicolegal implications of a Pharmacovigilance Risk Assessment Committee statement in cases of complications resulting from treatment. Particularly in EU countries where the Pharmacovigilance Risk Assessment Committee's recommendations carry much legal weight, any 'high dose' local vaginal treatment exceeding 4 weeks' duration may prove difficult to defend by a gynaecologist facing allegations of medical negligence in a case of breast cancer, for example. One may always quote the North American Menopause Society's opinion but in any country of the European Union, unless backed with serious scientific evidence to the contrary, the Pharmacovigilance Risk Assessment Committee's published advice is likely to override this.

Conclusions

The Pharmacovigilance Risk Assessment Committee should either publish its scientific evidence, backing its repeated statement, or else amend its advice with regard to caring for the postmenopausal woman with serious symptomatic genitourinary atrophy.

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