Signal

Desogestrel and Night sweats, vulvovaginal dryness and dry eye

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Summary

Night sweats, vulvovaginal dryness and dry eye are reported as adverse drug reactions to desogestrel, an oral contraceptive, in 53 individual case safety reports in VigiBase. There are 20 desogestrel – night sweats reports with 14 positive dechallenges, 22 desogestrel – vulvovaginal dryness reports with 12 positive dechallenges and 15 desogestrel – dry eye reports with 7 positive dechallenges. The reports, mostly provided by consumers, concern women 22 to 50 years old, where desogestrel was usually the only drug reported. Few reports provided any other possible explanation for the reactions. Several consumers described a significant negative affect on quality of life and noticeable improvement when discontinuing desogestrel. These three adverse drug reactions are already included in descriptions of some other contraceptives, but not for desogestrel, therefore it is important to communicate this signal.

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Introduction

During a joint patient report signal detection screening involving Uppsala Monitoring Centre and the Netherlands Pharmacovigilance Centre Lareb, an association between desogestrel and night sweats was identified. This revived interest in two desogestrel combinations that were identified in 2016 but were kept under review at the time. These were vulvovaginal dryness and dry eye in conjunction with desogestrel.

Desogestrel is marketed in some countries as a single ingredient oral contraceptive, whereas it is only used in fixed-dose combination products together with ethinyloestradiol in other parts of the world. This assessment focused on the reports where desogestrel was used as single ingredient.

Desogestrel achieves its contraceptive effect primarily by the inhibition of ovulation. Other effects include increased viscosity of the cervical mucus and decreased oestradiol levels, to one corresponding to the early follicular phase.[1] After intake, desogestrel is metabolized to its active metabolite, etonogestrel.[2] Like other progestogen-only drugs, desogestrel is best suited for use during breast feeding and for women who do not want to use oestrogens.[1]

Night sweats have been defined in several ways, all of which describes heavy sweating during the night. It is a common inconvenience during perimenopause and menopause. It can also be an adverse outcome of treatment with antidepressants and has been observed as a symptom in several diseases.[3]

Vulvovaginal dryness most commonly occurs when oestrogen levels are decreased. The cause is often perimenopause, but it can also occur during breast-feeding or as an adverse effect to treatment, such as anti-oestrogen cancer medicines, chemotherapy or oral contraceptives.[4]

Dry eye is a common condition affecting especially those older than 40 years. More women than men are affected and especially menopausal or pregnant women and those taking oral contraceptives or who are on hormone replacement therapy. Androgens and oestrogens have receptors in the lacrimal and meibomian glands and thereby influence production of tear film. Changes in sex hormone levels can affect functions of these glands and subsequently result in dry eye symptoms.[5]

These three adverse drug reactions (ADRs) affect different organs but they have a common denominator – they are frequently experienced by women during perimenopause or menopause and during other conditions when sex hormone levels are changed.

Reports in VigiBase

There were 53 reports of desogestrel and either night sweats, vulvovaginal dryness or dry eye in VigiBase at the time of the analysis, 11 November 2018. Based on the overall reporting of adverse reactions for desogestrel and of these three adverse reactions in VigiBase, the expected values for the number of reports on these combinations were 3.5 for night sweats, 0.35 for vulvovaginal dryness and 3.6 for dry eye, thus the associations were highlighted as disproportionally reported, by IC analysis (Table 1). Fifty-two reports came from nine European countries and one from Latin-America. Reporters in almost all cases (72%) were consumers. They concern women of similar age range from 22 to 50 years, median being 34, 32 and 33 for night sweats, vulvovaginal dryness and dry eye respectively (Table 1). Weight and height were provided in 22 reports, and BMI values were calculated showing normal weight for the majority of these patients, median being 21, 23 and 22 for night sweats, vulvovaginal dryness and dry eye reports respectively (normal weight BMI=18,5 to 24,9). In many cases desogestrel was the only drug reported, suggesting that affected patients were overall healthy women, not being treated for other medical conditions. Desogestrel was indicated for contraception in almost all reports where an indication was provided (Table 1). In one report with ADR night sweats, desogestrel was prescribed for endometriosis of ovary and in another with ADR vulvovaginal dryness the indication was premenstrual syndrome. The times to onset for all reactions were typically within the first two weeks of treatment.

In the 15 reports where desogestrel treatment was stopped, the majority had recovered (8) or were recovering (5) from the night sweats. The time for recovery was rarely provided but a few cases mention either a rapid or gradual recovery. One patient described that when she started taking the pill in the mornings, the problem with night sweats disappeared. Desogestrel was the only drug used in 15 of the reports. Selective Serotonin Reuptake

Inhibitors (SSRIs) which can cause night sweats were co-reported in three reports. The severity of the night sweats was sometimes captured in the reporter's comments. Several user stories tell of the vigorous sweating causing them to wake up during the night and depriving them of sleep. One desogestrel user reported "*I was not getting enough sleep due to waking each night dripping with sweat, overheating caused nightmares which were highly unpleasant.*" Hormone levels (sometimes oestrogen) were mentioned in a few reports and "hormone level abnormal" was reported as a reaction in one, but no laboratory values were provided. "*I believe it may also be why my oestrogen levels are still low*" said one reporter (consumer).

The treatment was stopped in 13 cases, leading to improvement of vulvovaginal dryness in 11 cases, seven recovered and four recovering. In seven reports there were no stop dates for desogestrel suggesting continuation of treatment, of these five patients continued to suffer from the reaction. One of these accounts describes how the ADR had affected her life "*Patient then declares having menstrual bleeding every 15 days and vaginal dryness with increasing severity over time. (…) In the light of the consequences on the patient's personal life (discomfort and impossible sexuality), she took the decision herself to stop contraception. Effects disappeared immediately*". (translation from French).

Reporters provided information about stopping the drug in 11 cases of dry eye with the outcome recovered in four patients and recovering for three. One of the patients who stopped taking the drug and recovered, started to use Mirena (a contraceptive containing another progestogen - levonorgestrel) which led to the reappearance of the ADR. Three patients provided descriptions of the substantial negative impact this ADR had had on their lives. One of them wrote "*It's been so bad that I have been completely dependent on artificial tear fluid, and also used eye ointment at night. It has influenced my life to a large degree.... [I] would never have thought that quitting [treatment] would make the situation so much better. Noticed fairly immediately difference when I stopped, went from being completely dependent of eye drops, to not use them anymore!*" (translation from Norwegian).

Literature and Labelling

Night sweats, vulvovaginal dryness and dry eye are not mentioned among possible adverse reactions to desogestrel in the UK Summary of Product Characteristics (SmPC).[1] Nor does the patient information leaflet mention these three reactions.[6] The SmPC does cover one uncommon adverse reaction within the MedDRA system organ class Eye disorders: contact lens intolerance. Vaginal infection is listed as an uncommon adverse reaction for the vaginal tract.[1,6]

Table 1. Characteristics of case reports in VigiBase of reaction in association with desogestrel

	Night sweats	Vulvovaginal dryness	Dry eye
Number of reports	20	22*	15*
No of reporting countries	6	9	5
No reports with only desogestrel	15	15	10
Number of expected reports	3.5	0.35	3.6
IC_{025}	1.66	3.97	1.10
Age, median (range)	34 (24 - 46)	32 (22 - 50)	33 (22 - 46)
BMI, median (range)	21 (19 - 27)	23 (18- 28)	22 (21- 29)
Indication – contraception	16	18	11
Time-to-onset, median (range)	15 (1-49 days)	7 (0 days-7 years)	2 (0 days-2 months)
Outcome, Recovered or Recovering	17	13	9
Positive dechallenge	14	12	7

**Four reports had both ADR terms vulvovaginal dryness and dry eye*

On the other hand, ADRs set out in this analysis are listed among ADRs for some combined contraceptives, which contain ethinylestradiol and a progestogen. These are products containing ethinylestradiol and norgestimate, which have night sweats, vulvovaginal dryness and dry eye in the label.[7] Products containing ethinylestradiol and drospirenone, have vaginal dryness and dry eye labelled.[8] Nuvaring contains ethinylestradiol and etonogestrel, the active metabolite of desogestrel, and has vulvovaginal dryness labelled.[9] The National Health Service in the UK lists contraceptive pills as one of the causes of vaginal dryness.[10] Contraceptive pills are also mentioned among the factors that can contribute to dry eye by the National Eye Institute of the USA.[11]

Discussion and Conclusion

Desogestrel is known to decrease oestrogen level and it might be this effect that plays a role in the development of the menopausal symptoms in these cases. They could also potentially be explained as naturally occurring perimenopause, a state when sex hormonal levels start to change, decreasing oestradiol levels being one them. Most women in this case series were of premenopausal age, ranging between 22-50 years with a median for all three reactions of 33 years. The average age at which menopause occurs is 51 years and perimenopause usually start after mid-40s, but some women already experience it in their mid-30s.[12] However, in most cases the onset of symptoms came soon after beginning of desogestrel treatment and the majority of desogestrel users saw the symptoms disappear after dechallenge, which argues against perimenopause.

Another potential risk factor leading to low oestrogen levels and associated symptoms is low weight, but available BMI values show that only one patient's weight was below the normal range (BMI= <18,5). Few other medicines were taken concomitantly and therefore co-medication could not explain these reactions either. Another possible cause of one of the reactions, vulvovaginal dryness, is breast-feeding which is mentioned in two reports in the vulvovaginal dryness case series.

The three reactions discussed here have already been listed for some other contraceptives. Night sweats and vulvovaginal dryness have also been reported in VigiBase more often than expected for other progestogens (levonorgestrel, medroxyprogesterone and norethisterone), suggesting potential class effects. Tamoxifen, an anti-oestrogen used in breast cancer treatment, also causes menopausal symptoms, night sweats and vaginal dryness being two of them.[13]

The SmPC of desogestrel lists ADRs contact lens intolerance and vaginal infection. A common reason for not being able to use contact lenses is having dry eyes. Likewise, one of risk factors for vaginal infection is vaginal dryness. Therefore, although vulvovaginal dryness and dry eye are not labelled, they might be the underlying causes or parts of these symptoms, where a connection may be obvious for a health care professional, but not for a consumer. This may be the reason why vulvovaginal dryness and dry eye are mostly reported by consumers.

In conclusion, in looking at research literature, SmPCs and health online resources, vulvovaginal dryness and dry eye are already associated with use of contraceptive drugs. These case series present a short time to onset of symptoms, many positive dechallenges, not many confounders, and there is a possible mechanism behind the reactions. In addition, patients in the case series tell of vigorous sweating, vaginal dryness affecting sexual activity and being completely dependent on artificial tear fluid. Considering the consequences for the patient these reactions may cause, it is important to communicate this signal.

References

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7. Electronic Medicines Compendium: Summary of Product Characteristics for Cilique 250/ 35 microgram tablets (https://www.medicines.org.uk/emc/product/2011) Accessed: March 2019

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9. Electronic Medicines Compendium: Summary of Product Characteristics for Nuvaring (https://www.medicines.org.uk/emc/product/6449) Accessed: March 2019

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11. National Eye Institute: Dry Eye https://nei.nih.gov/health/dryeye/dryeye Accessed: March 2019

12. National Health Service: Menopause https://www.nhs.uk/conditions/menopause/ Accessed: September 2019

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SIGNAL

WHO defines a signal as:

"Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously". An additional note states: "Usually more than one report is required to generate a signal, depending on the seriousness of the event and the quality of the information".*

A signal is therefore a hypothesis together with supporting data and arguments. A signal is not only uncertain but also preliminary in nature: the situation may change substantially over time one way or another as more information is gathered. A signal may also provide further documentation of a known association of a drug with an ADR, for example: information on the range of severity of the reaction; the outcome; postulating a mechanism; indicating an "at risk" group; a dose range which might be more suspect; or suggesting a pharmaceutical group effect or a lack of such an effect by a particular drug.

Signals communicated by UMC are derived from VigiBase, the WHO global database of individual case safety reports. This database contains summaries of individual case safety reports of suspected adverse drug reactions, submitted by national pharmacovigilance centres (NCs) that are members of the WHO Programme for International Drug Monitoring. More information regarding the status of this data, its limitations and proper use, is provided in the Caveat on the last page of this document.

VigiBase is periodically screened to identify drug-ADR combinations that are unknown or incompletely documented. Combinations of such interest that they should be further reviewed clinically are sent to members of the Signal Review Panel for in-depth assessment. The Signal Review Panel consists of experienced international scientists and clinicians, usually affiliated with a governmental or an academic institution. The expert investigates the clinical evidence for the reaction being related to the suspected drug.

The topics discussed in the signals represent varying levels of suspicion. Signals contains hypotheses, primarily intended as information for the national regulatory authorities. They may consider the need for possible action, such as further evaluation of source data, or conducting a study for testing a hypothesis.

The distribution of signals is currently restricted to NCs, regulatory authority staff and their advisers, participating in the WHO Programme. Signals are sent to the pharmaceutical companies when they can be identified as uniquely responsible for the drug concerned. UMC does not take responsibility for contacting all market authorisation holders. As a step towards increased transparency, since 2012 UMC signals are subsequently published in the WHO Pharmaceuticals Newsletter.

National regulatory authorities and NCs are responsible for deciding on action in their countries, including communicating the information to health professionals, and the responsible market authorisation holders, within their jurisdiction.

In order to further debate, we encourage all readers of signals to comment on individual topics.

* Edwards I.R, Biriell C. Harmonisation in pharmacovigilance. Drug Safety 1994;10:93-102.

Responses from industry

Signals on products under patent are submitted to patent holders for comments. Responses from industry are unedited. The calculations, analysis and conclusions are theirs, and should be given serious but critical consideration in the same way as any scientific document. The WHO and UMC are not responsible for their findings, but may occasionally comment on them.

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Caveat Document

Statement of reservations, limitations and conditions relating to data released from VigiBase, the WHO global database of individual case safety reports (ICSRs). Understanding and accepting the content of this document are formal conditions for the use of VigiBase data.

Uppsala Monitoring Centre (UMC) in its role as the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring receives reports of suspected adverse reactions to medicinal products from National Centres in countries participating in the WHO Programme for International Drug Monitoring. The information is stored in VigiBase, the WHO global database of individual case safety reports (ICSRs). It is important to understand the limitations and qualifications that apply to this information and its use.

Tentative and variable nature of the data

Uncertainty: The reports submitted to UMC generally describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a specific medicinal product is the cause of an event, rather than, for example, underlying illness or other concomitant medication.

Variability of source: Reports submitted to national centres come from both regulated and voluntary sources. Practice varies: some national centres accept reports only from medical practitioners; others from a broader range of reporters, including patients, some include reports from pharmaceutical companies.

Contingent influences: The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the adverse effects and other factors.

No prevalence data: No information is provided on the number of patients exposed to the product, and only a small part of the reactions occurring are reported.

Time to VigiBase: Some national centres make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not. Time from receipt of an ICSR by a national centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from that obtained directly from national centres.

For these reasons, interpretations of adverse effect data, and particularly those based on comparisons between medicinal products, may be misleading. The data comes from a variety of sources and the likelihood of a causal relationship varies across reports. Any use of VigiBase data must take these significant variables into account.

Prohibited use of VigiBase Data includes, but is not limited to:

- patient identification or patient targeting
- identification, profiling or targeting of general practitioners or practice

Any publication, in whole or in part, of information obtained from VigiBase must include a statement:

(i) recording 'VigiBase, the WHO global database of individual case safety reports (ICSRs)' as the source of the information

(ii) explaining that the information comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases

(iii) affirming that the information does not represent the opinion of the UMC or the World Health Organization.

Omission of this statement may exclude the responsible person or organization from receiving further information from VigiBase.

UMC may, in its sole discretion, provide further instructions to the user, responsible person and/or organization in addition to those specified in this statement and the user, responsible person and/or organization undertakes to comply with all such instructions.

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