

Analysis of Spontaneous Reports of Thromboembolic Adverse Drug Reactions Associated with Cyproterone/Ethinylestradiol

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Introduction: After media attention on thromboembolic adverse drug reactions (ADRs) and the use of cyproterone/ethinylestradiol [1], the Netherlands Pharmacovigilance Centre Lareb received a high number of reports about this association, which called for a more detailed analyses.

Aim: To provide an overview of the characteristics of all reports of thromboembolic ADRs associated with the use of cyproterone/ethinylestradiol submitted to Lareb until April 3rd 2013 focusing on character, circumstances, off-label use and degree of recognition of the ADRs.

Methods: Reports were selected from the Lareb database based on ATCcode G03HB01 using an MS Access_ query. Lareb analysed the reporter type, seriousness of the reaction according to the CIOMS criteria, patient's age at the occurrence of the ADR, patient's BMI (kg/m²), indication, ADRs classified as arterial thrombosis (including MedDRA_ Preferred Terms like myocardial infarction, transient ischemic attack), venous thrombosis, pulmonary embolism or unspecified thrombosis, latency period, outcome of the reaction, treatment of the ADR, delay between the first symptoms and diagnosis of the ADR, presence of risk factors including smoking and Factor-V-Leiden deficiency.

Results: On April 3, 2013 Lareb had received a total of 621 reports about cyproterone/ethinylestradiol, including 309 reports of thromboembolic ADRs which were further analysed. Reported ADRs consisted of arterial thrombosis (N = 52), venous thrombosis (N = 40), pulmonary embolism (N = 155) and thrombosis with an unspecified location (N = 128). A total of 299 reports of thromboembolic ADRs were classified as serious, including 18 cases with a fatal outcome. Patient's mean age was 30.5 years and mean BMI was 24.3 kg/m². The primary indications for use were acne (N = 147), oral contraceptive (N = 122), hirsutism (N = 10), other (N = 15) or the indication was unknown (N = 15). Of the 309 patients with a thromboembolic ADR, 261 were known to have been treated with anticoagulant drugs. In 31 cases the thromboembolic ADR was initially not recognized as such by either the patient or their healthcare professional. The median time to onset was 2–3 years, however many patients reported a longer latency period. There was no distinction between the time of onset in respect to the reported ADR. No differences in risk factors seem to exist between labeled and off-label indications. In 291 out of 309 reports, the reporter was a consumer.

Conclusions: The reported thromboembolic ADRs are a known risk related to the use of cyproterone/ethinylestradiol, but may be misdiagnosed initially. From the reports that Lareb received it is evident that off label use is frequent.

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