Combined used of tranexamic acid and combined hormonal contraception and potential risk of thrombo-embolic events

Introduction

Tranexamic acid (Cyklokapron®) is indicated for adults and children over the age of 1 year, for *prevention and treatment of bleedings due to general or local fibrinolysis, and for hereditary angioedema.* It is a competitive inhibitor of plasminogen, preventing the formation of plasmin in the fibrinolytic system. It is available in three administration forms; a tablet (500 mg), an injection (100mg/ml). Tranexamic acid was granted market authorization in the Netherlands in 1968 [1,2]. In addition, tranexamic acid is also available as a mouth wash (magistral preparation), which is indicated for *a high risk of bleeding during dental procedures, during use of direct oral anticoagulantia (DOACs) or vitamin-K antagonists*. This report does not focus on the mouth wash.

Combined hormonal contraception drugs are known to give an increased risk of thrombo-embolic events. In the Dutch Summary of Product Characteristics (SmPC) of the tranexamic acid injections [1,3-7] and
the Dutch SmPC of tranexamic acid (Tillomed®) 500 mg tablets [8] the following is included:

- *Section 4.4: Due to the increased risk of thrombosis, tranexamic acid needs to be administrated with caution in patients using oral contraceptives (see section 4.5).*
- *Section 4.5: Drugs that have a mechanism of action on the hemostasis need to be administrated with caution in patients treated with tranexamic acid. There is a theoretical risk of thrombosis, like with estrogens.*

These cautions are not mentioned in the SmPC of tranexamic acid tablets 500 mg from Sandoz or Cyklokapron® [2,8].

Reports

The Netherlands Pharmacovigilance Centre Lareb received one report (NL-LRB-00351184, Sept. 2019) from a consumer concerning a woman aged 50-60 years, with pulmonary embolism, myocardial infarction, and pulmonary infarction 48 hours after administration of tranexamic acid (Cyklokapron®) tablets 500 mg indicated for vaginal bleeding. The tranexamic acid was withdrawn and the patient recovered with sequelae; chronic small pulmonary embolies, chronic pleural pain, and regular pleuritis. As a concomitant drug, the patients used ethinylestradiol/levonorgestrel tablet 30/150 ug, for an unknown indication. No other risk factors for thrombo-embolic events were reported. The patient had a BMI of 20.8.

Lareb received three other reports concerning tranexamic acid and thrombo-embolic complications. In these reports (NL-LRB-95119, NL-STADA-033310, and NL-LRB-235391), combined hormonal contraception drugs were not reported as concomitant medication. In report NL-LRB-235391 lynestrenol is used as concomitant medication. Lynestrenol is a progestagen. The SmPC describes [10]: ‘Although the clinical relevance for the risk of development of thrombo-embolic events with the use of a progestagen without the estrogen component is unknown, lynestrenol should be discontinued in women who develop a thrombo-embolic event’. Report NL-LRB-235391 was made by a specialist doctor and concerns a woman aged 30-40 years, with pulmonary embolism following a possible drug interaction between lynestrenol for unknown indication and tranexamic acid for vaginal haemorrhage due to uterine leiomyoma with a latency of 5 days after start. The drugs lynestrenol and tranexamic acid were withdrawn. The patient was treated with acenocoumarol. At time of reporting, 1 day after start of the event, the patient was recovering. Concomitant medication was not reported. The medical history indicates that the patient had uterine leiomyoma. The patient has no known past drug therapy.

Other sources of information

SmPC

The US product label of tranexamic acid tablets (Lysteda®) describes as a contraindication for the use of the drug in combination with oral contraceptives due to the thrombo-embolic risk: ‘Do not prescribe tranexamic acid tablets to women who are using combination hormonal contraception’ [11].

Literature

In literature one case was found in which a 42 year old woman experienced thrombosis in a coronary vessel after combined use of tranexamic acid injections 3 times daily and an oral contraceptive pill (ethinylestradiol 20 mcg and gestodene 75 mcg) [12]. Throne et al. [13] reviewed the literature concerning the question 'Heavy menstrual bleeding: is tranexamic acid a safe adjunct to combined hormonal contraception?'. Concerns about an increased risk of venous thromboembolism (VTE) when combined hormonal contraception and tranexamic acid are used in combination are not supported by long term clinical experience. VTE in women using combined hormonal contraception is a rare but serious event. They mention that tranexamic acid does not increase the risk of development of a VTE, but its antifibrinolytic activity would reduce the chance for spontaneous resolution of the thrombosis. They concluded that the extensive clinical experience demonstrating the safety of short term tranexamic acid exposure and its very beneficial effects for acute heavy menstrual bleeding suggest that the benefits of therapy even when combined with combined hormonal contraception for most women will outweigh potential risks. Women with increased risks for VTE beyond the risk conferred by combined hormonal contraception (immobility, obesity, coagulopathy, etc.) should probably avoid this combination therapy.

Database

Table 2. Prescription data (number of users [14])

Drug	2014	2015	2016	2017	2018
Tranexamic acid	16.138	16.961	18.922	20.432	23.550

Mechanism

Tranexamic acid prevents the formation of plasmin in the fibrinolytic system. Fibrinolysis is an enzymatic process that dissolves the fibrin clot into fibrin degradation products by plasmin originating from fibrin bound plasminogen in the liver. In women with menorrhagia, fibrinolytic activity is high, likely due to high levels of plasmin and plasminogen activators from the endometrium [15-16].

Estrogen-containing medication is associated with changes in the hemostatic balance and gives an increased risk of the development of thrombo-embolic events. The use of combined hormonal contraceptive drugs is associated with increased levels of plasma-circulating pro-coagulant factors such as fibrinogen, prothrombin, factor VII, VIII, and X. The use of combined hormonal contraceptives also results in decreased plasma levels of naturally occurring inhibitors of hemostasis such as anti-thrombin and tissue factor pathway inhibitors. These factors all contribute to an increased risk of the development of thrombo-embolic events [17].

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received one report of thrombo-embolic events associated with the use of tranexamic acid in which the patient also used combined hormonal contraception. A warning for combined use of tranexamic acid and combined hormonal contraception is mentioned in the Dutch SmPC of most tranexamic acid products. Such a warning is however not included in the Dutch SmPC of tranexamic acid tablets 500 mg Sandoz or Cyklokapron®. The increased risk of thrombo-embolic events can be explained by the mechanisms of how both drugs interfere with the fibrinolytic system and hemostatic balance. Thrombo-embolic events can be serious, resulting in hospitalization and even death. It is for this reason important that healthcare professionals and patients are aware of this possible risk of combined use of these drugs.

References

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This signal has been raised on July 27, 2020. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl