EDITORIAL

Medication and venous thromboembolism: a complex interaction

S. Schol-Gelok[1]*, M.J.H.A. Kruip[2], J. Versmissen[1]

[1]Department of Hospital Pharmacy and Internal Medicine, Erasmus University Medical Center, Rotterdam, the Netherlands, [2]Department of Haematology, Erasmus University Medical Center, Rotterdam, the Netherlands, *corresponding author: email: s.schol-gelok@erasmusmc.nl

In the pathogenesis of venous thromboembolism (VTE) three main components were identified by Virchow, a nineteenth century German physician: alterations in blood coagulation, diminished blood flow or damage of the vascular endothelium, or a combination of these factors.[1] Risk factors of VTE such as immobility, active infection or cancer, pregnancy, trauma, advanced age, antiphospholipid antibodies, obesity and certain genetic traits such as the factor V Leiden mutation all influence one or more of these three components.[2] Additionally, it has gradually become clear that many drugs can lower or increase the risk of VTE through different mechanisms influencing the triad of Virchow.

Antiplatelet drugs, such as aspirin and clopidogrel, inhibit thrombocyte aggregation and decrease thrombus formation. As expected, they reduce the risk of VTE and have been considered as secondary prevention in patients with VTE.[3] Other, less expected groups of drugs may also lower the risk of thrombosis. HMG-CoA reductase inhibitors for example, more commonly known as statins, lead to a lower risk of venous thrombosis, as confirmed in a recent meta-analysis of intervention studies: the risk of a primary venous thrombosis was 15% lower in the statin-treated group.[4] This is probably due to inhibition of geranylgeranylation of the Rho/Rho kinase pathway as one of the key mechanisms of the anticoagulant effects.[5,6]

During the 1990s it became strikingly obvious that certain drugs could also increase the risk of VTE. Based on several case series describing an association between oral contraceptives and a higher risk of VTE, a large case-control study was eventually performed by the World Health Organization (WHO). This study confirmed a two- to four-fold increase of the risk of VTE in oral contraceptive users, particularly with third generation contraceptives.[7] A riot ensued when both the German Federal Institute for drugs and medical services and the British government initially discouraged the use of third generation oral contraceptives because of this increased risk of VTE. The European Medicines Agency (EMA) and Food and Drug Administration (FDA), on the other hand, had decided that these drugs should not be withdrawn. This resulted in many more studies, which were evaluated in a Cochrane review in 2014, finally concluding that oral contraceptive users did indeed run a higher risk of VTE, while the risk third generation users ran was only slightly higher than that of second generation users.[8] Glucocorticoids, another class of commonly prescribed drugs, are also well known for their increased risk of thrombosis, as expected by their working mechanism, which leads to increased levels of clotting factors and fibrinogen.[9] Based on their working mechanism, other, less frequently prescribed medications are also expected to increase the risk of VTE. For example, anti-epidermal growth factor receptor (EGFR) agents, classified as either monoclonal antibodies (MoAbs) or tyrosine kinase inhibitors (TKIs) are both associated with a significant increase of the risk of VTE.[10] The most difficult associations to detect are in the groups of drugs that unexpectedly increase the risk of VTE. In this issue of the *NJM* Dijkstra and Van der Weiden et al. describe a case of a schizophrenic patient who was diagnosed with a deep venous thrombosis six months after starting olanzapine. The authors found disproportionate Reporting Odds Ratios (RORs) in the global database for adverse drug reactions for VTE and olanzapine. The mechanism behind this association seems to be multifactorial, with lethargy and weight gain after starting olanzapine treatment being the most likely risk factors in the development of VTE.

The ROR has been developed as a hypothesis generating tool for the detection of signals of an association between a certain drug and a side effect.[11] It is based on spontaneous reporting from various resources to the pharmacovigilance databases such as the Netherlands Pharmacovigilance Centre of Lareb and the worldwide Vigilyze pharmacovigilance database maintained by the WHO collaborating centre for international drug monitoring. As shown by

the publication of several case series about the association between oral contraceptives and the higher risk of VTE, it remains vital that physicians keep reporting to pharmacovigilance databases any unexpected case of VTE that might be related to a certain drug. This will increase our knowledge of the risk of thrombosis and possibly prevent new events.

REFERENCES

1. Bagot CN, Arya R. Virchow and his triad: a question of attribution. Br J Haematol. 2008;143:180-90.
2. Anderson FA Jr, Spencer FA. Risk factors for venous thromboembolism. Circulation. 2003;107:9-16.
3. Cohen AT, Imfeld S, Markham J, Granziera S. The use of aspirin for primary and secondary prevention in venous thromboembolism and other cardiovascular disorders. Thromb Res. 2015;135:217-25.
4. Kunutsor SK, Seidu S, Khunti K. Statins and primary prevention of venous thromboembolism: a systematic review and meta-analysis. Lancet Haematol. 2017;4:e83-e93.
5. Violi F, Calvieri C, Ferro D, Pignatelli P. Statins as antithrombotic drugs. Circulation. 2013;127:251-7.
6. Oesterle A, Laufs U, Liao JK. Pleiotropic Effects of Statins on the Cardiovascular System. Circ Res. 2017;120:229-43.
7. Venous thromboembolic disease and combined oral contraceptives: results of international multicentre case-control study. World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Lancet. 1995;346:1575-82.
8. de Bastos M, Stegeman BH, Rosendaal FR, et al. Combined oral contraceptives: venous thrombosis. Cochrane Database Syst Rev. 2014:CD010813.
9. Johannesdottir SA, Horvath-Puho E, Dekkers OM, et al. Use of glucocorticoids and risk of venous thromboembolism: a nationwide population-based case-control study. JAMA Intern Med. 2013;173:743-52.
10. Petrelli F, Cabiddu M, Borgonovo K, Barni S. Risk of venous and arterial thromboembolic events associated with anti-EGFR agents: a meta-analysis of randomized clinical trials. Ann Oncol. 2012;23:1672-9.
11. Kabel JS, van Puijenbroek EP. [Side effects of tramadol: 12 years of experience in the Netherlands]. Ned Tijdschr Geneeskd. 2005;149:754-7.