Acta Ophthalmologica

Severe epistaxis related to intravitreal bevacizumab

Leila S. Otten,[1]
Madelon H. Butterhoff-Terlingen,[2]
Verena C. Mulder,[3,4]
Willemien Lagas- de Graaf,[2]
Angela M. van der Hage-Lie[5] and
Paul D. van der Linden[2]

[1]Department of Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands; [2]Department of Clinical Pharmacy, Tergooi Hospital, Hilversum, The Netherlands; [3]Rotterdam Ophthalmic Institute, Rotterdam Eye Hospital, Rotterdam, The Netherlands; [4]Department of Clinical Pharmacy, Franciscus Gasthuis & Vlietland, Rotterdam, The Netherlands; [5]Department of Ophthalmology, Tergooi Hospital, Hilversum, The Netherlands

doi: 10.1111/aos.14176

Editor,

Multiple anti-VEGFs have been developed for the management of ocular indications like age-related macular degeneration (AMD), such as ranibizumab (IVR) (Lucentis®, Genentech, San Fransisco, California, United States and Novartis, Basel, Switzerland) and aflibercept (Eylea®, Regeneron, Tarrytown, NY, United States and Bayer, Berlin, Germany). Intravitreal bevacizumab (IVB) is broadly used off-label in wet AMD because of comparable efficacy and safety profile and lower costs than registered anti-VEGFs (Elshout et al. 2014). There are several known ocular complications of IVB use (Biagi et al. 2014). Reports of systemic adverse events (AEs) are, however, scarce. We report the first case of severe epistaxis probably related to IVB use.

A 95-year-old woman was found by her husband at home in a confused status with severe epistaxis. She had suffered from another severe epistaxis the previous evening. One day before that first epistaxis, IVB was administered. She was transferred to the emergency department (ED) of the local hospital and admitted after thorough examination. During hospitalization, episodes of epistaxis continued approximately once to twice daily despite first-aid measures. The duration of these episodes varied from a few to twenty minutes. Because her clinical status neither improved nor worsened, the patient was discharged after 6 days of hospitalization. One week after discharge the epistaxes were still ongoing, and the Kiesselbach's plexus on the right side was cauterized. Two and a half weeks later, the patient was readmitted to the ED with a cerebral infarction. Treatment with clopidogrel was initiated. During this hospitalization, IVB was administered but no epistaxis reoccurred.

Her past medical history besides AMD included: heart failure, goitre and transient ischaemic attack, which were controlled by oral medication, but no anticoagulants. Her AMD was treated with IVB, every 4–8 weeks 1.25 mg in both eyes and had started 9 months prior to current events. There were no previous epistaxes reported to her GP. She was suffering from anaemia and stomach ache since a couple of months, which were attributed to possible gastrointestinal bleedings that might indicate a haemostatic imbalance. This was being treated with pantoprazole and ferrous fumarate, but no gastroscopy was performed.

Haemorrhagic disturbances like thromboembolisms and epistaxes are very common after intravenous administration of bevacizumab and are caused by multifactorial processes that include erythropoietin overproduction, vascular integrity damage and thrombocytopenia (Kamba & McDonald 2007). However, systemic AEs are pharmacokinetically unexpected after IVB administration since the blood-ocular barriers separate the compartment of the eye from systemic circulation. Hence, it seems likely that patients or physicians do not relate epistaxes to IVB. Studies that assessed the systemic safety of IVB report inconclusive results. A systematic review concluded that the incidences of serious AE between the different intravitreal anti-VEGFs were similar (Van der Reis et al. 2011). However, a more recent systematic review evaluating the safety of IVB by pooling clinical trial data found significantly higher serious systemic AE rates in the IVB group compared with the IVR group (n = 1795, RR = 1.27 and CI = 1.09–1.47) (Poku et al. 2014). Another pharmacovigilance study analysed AEs reported in the WHO database (Biagi et al. 2014). This study concluded that after IVB administration ocular infections were paramount compared with IVR or intravitreal pegabtanib, probably due to an extra compounding procedure. It should be noted that included studies in the systematic reviews mostly weren't powered to assess safety and that pharmacovigilance studies are regularly biased through selective reporting and underreporting.

In conclusion, the safety profile of IVB remains unclear. More intense monitoring of patients and studies of systemic safety are needed to define the safety profile of IVB.

References

Biagi C, Conti V, Montanaro N et al. (2014): Comparative safety profiles of intravitreal bevacizumab, ranibizumab and pegaptanib: the analysis of the WHO database of adverse drug reactions. Eur J Clin Pharmacol **70**: 1505–1512.

Elshout M, van der Reis MI, Webers CAB & Schouten JSAG (2014): The cost-utility of aflibercept for the treatment of age-related macular degeneration compared to bevacizumab and ranibizumab and the influence of model parameters. Graefe's Arch Clin Exp Ophthalmol **252**: 1911–1920.

Kamba T & McDonald DM (2007): Mechanisms of adverse effects of anti-VEGF therapy for cancer. Br J Cancer **96**: 1788–1795.

Poku E, Rathbone J, Wong R, Everson-Hock E, Essat M, Pandor A & Wailoo A (2014): The safety of intravitreal bevacizumab monotherapy in adult ophthalmic conditions: systematic review. BMJ Open **4**: e005244.

Van der Reis MI, La Heij EC, De Jong-Hesse Y, Ringens PJ, Hendrikse F & Schouten JSAG (2011): A systematic review of the adverse events of intravitreal anti-vascular endothelial growth factor injections. Retina **31**: 1449–1469.

Correspondence:
Leila S. Otten, BS
Department of Pharmaceutical Sciences
Utrecht University
Utrecht
The Netherlands
Tel: +31654790555
Email: leilasophieotten@gmail.com