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Adverse effects of immunoglobulin G therapy: thromboembolism and haemolysis

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Immunoglobulin (Ig) G replacement therapy is well tolerated by the majority of recipients; however, isolated or recurrent adverse events occur in about a third of patients. Thrombosis has been a recognized complication of IgG infusion for the past 20 years [1]. All forms of thrombotic disease have been recognized including, but not limited to, thrombotic microangiopathy, deep vein thrombosis, myocardial infarction, stroke, pulmonary embolism and transfusion-related acute lung injury (TRALI). These are thought to occur more often with intravenous (i.v.) infusion, but are also associated more rarely with subcutaneous (s.c.) therapy.

In 2010, the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA) identified individuals in a health-care database who had received IgG therapy ($n = 11\,785$) and had a thrombotic event on the same day, with the aim of ascertaining the frequency of these thrombotic events and the differences in frequency, if any, between IgG products [2]. Between January 2008 and September 2010, approximately 1% of the study population ($n = 122$) experienced thromboembolic adverse events (TAEs); the per-infusion rate, although not investigated, would be lower because patients received multiple infusions during the study time-frame. Variances in rates of TAEs between different IgG products were also noted, with an approximately three-fold variation overall. The extension of the retrospective study (2008–11) looked at hyperimmune globulin products; the overall rate of TAEs was reported at one-tenth of that in the initial study (< 0·01%); however, the highest rates were very similar to those observed previously [3].

The predominant mechanism responsible for these TAEs is thought to involve activated factor XIa. In 2010, an investigation following a cluster of TAEs associated with a single IgG product [4] identified activated factor XIa as a probable procoagulant contaminant. Significant levels of factor XIa have been found in all cases where gammaglobulin preparations associated with thrombosis have been studied; other possible procoagulant contaminants have also been found, but their roles are yet to be defined. Differential content of factor XIa between IgG products correlates with the observance of TAEs, and those products associated with the highest rates of TAEs have the highest level of factor XIa activity. However, this activity alone does not completely predict TAEs; these have been seen to occur with products containing relatively low factor XIa levels and vice versa. Researchers from the Paul Ehrlich Institute studied levels of factor XI antigen and factor XIa activity in batches of IgG which had been associated with TAEs [5]. Relatively high levels of both the antigen and activity were seen in these batches, while relatively low levels were seen in other batches and also products from different manufacturers. However, there were batches of IgG which appeared to have high levels of factor XI antigen and factor XIa activity, but were not associated with TAEs [5].

The current standard for measuring the thrombogenic potential of IgG is a thrombin generation assay with reference to a plasma standard, and this usually correlates well with the amount of factor XIa found in the product [6]. The non-activated partial thromboplastin time (NAPTT) is also used as a measure of thrombogenic potential; however, it is less sensitive. This assay also tends to have a good correlation with factor XIa activity within batches of IgG [6].

Research has also been conducted to assess potential risk factors for TAEs in patients receiving IgG therapy. A retrospective study [7] looking at 62 neurology patients in a single institution recorded seven TAEs across 616 infusions within a 2-year period, and five of these occurred within 14 days of IgG administration. In these five patients, two independent risk factors were identified: immobility and coronary artery disease. A variety of other potential risk factors were also observed including male gender, old age, diabetes, dyslipidaemia, hypertension, family history of thrombosis and atrial fibrillation. Patients who had four or more of these had a significantly higher risk in this cohort [7]. A broader review of the literature [8] identified further potential risk factors, including disproteinaemia, smoking, history of thrombosis, anaemia/polycythaemia, oestrogen use and a

hypercoagulable state. Most TAEs occur after large-dose infusions, while first infusions and rapid infusions are also associated with higher rates of TAEs. It has been proposed that strategies such as prehydration or premedication can ameliorate the risk; however, further investigations are required to confirm this.

In addition to thrombotic events, in certain cases haemolysis has also been identified as another serious complication of IgG use. The FDA estimates that approximately one in 10 000 infusions are associated with haemolytic complications, but the recognition of these is thought to be delayed in more than 50% of cases. The main complication is severe anaemia, usually requiring transfusion, while acute renal failure and deaths have also been reported. These are thought to occur almost exclusively with i.v. therapy.

The Canadian IVIg haemolysis pharmacovigilance group defines haemolytic events associated with IgG infusion as being a drop in haemoglobin of ≥10 g/l, a positive result in a direct anti-globulin test and at least two of the following within 10 days of IgG infusion: increased reticulocyte count; increased lactate dehydrogenase level; low haptoglobin level; unconjugated hyperbilirubinaemia; haemoglobinaemia; haemoglobinuria; or the presence of significant spherocytosis [9–11].

There has been a large increase in reports of haemolysis to the Canada vigilance programme in the last 3 years; it is not clear whether this is due to increased IgG use, changes in prescribing practice, higher dose infusions or increased vigilance. Desborough *et al.* [11] reviewed all published cases of haemolysis following IgG infusion and also reports made to vigilance authorities in North America and Europe between January 1998 and May 2012. They documented 925 reported cases and 34 recorded deaths in these individuals. If every death was associated with the reported haemolytic event, this would represent a case fatality rate of 0·3%; however, the review does not confirm whether or not this is the case.

The predominant mechanism thought to be responsible for haemolysis following IgG therapy involves anti-A or anti-B isoagglutinins in gammaglobulin preparations. As type O is the most predominant blood type across all ethnic groups, it is logical to assume that anti-A and anti-B isoagglutinins will be found in significant concentrations in a pooled plasma product. The review by Desborough *et al.* [11] investigated 62 published cases of haemolysis, and of these identified 40 in patients with blood type A and 16 in patients with type AB, indicating the importance of type A as a target antigen in these patients. The presence of one reported case in a type B patient, and another with type O, suggest that haemolysis could also have been associated with other specificities such as anti-D. Almost all cases were reported in patients receiving high-dose anti-inflammatory IgG therapy. It should be noted that death directly associated with haemolysis did not occur in these reported cases.

The principal risk factor for haemolysis is non-O blood type. Antigen density on red blood cells may be another risk factor, as may the non-secretor phenotype. Further investigation is required to ascertain whether non-A/B antibodies contribute. Macrophage activation and inflammation are also probably implicated, and pre-existing haemolytic disease may be another risk factor. The events also occur more frequently after high-dose infusion, >1·5–2 g/kg over 1–5 days, with 45% of reported cases occurring after a 2–3 g/kg dose.

Currently, specifications for IgG products in the United States and the European Union set an antibody limit of ≤1:64 in a direct haemagglutinin assay [12], and precautionary labelling of these products is also in use. Research is currently ongoing to identify ways to reduce the amount of agglutinin in the final product: affinity extraction is currently under investigation, but is not yet widely used. It is also important to monitor the fraction of type O donors contributing to the product, as a larger proportion of type O will lead to a larger proportion of agglutinins in the final product. Given the large size of the type O donor population, it is difficult to exclude them from the pooled plasma pool; however, it is possible to screen plasma donors for high anti-A titres [13]. Other ways to prevent haemolysis include prescreening patients for active haemolysis, modifying the dose/rate regimen (for example, using the lowest effective dose, infusing slowly), pretreatment with steroids to reduce macrophage activation and increased monitoring post-infusion.

While IgG is well tolerated by the vast majority of patients, thromboembolic and haemolytic events can occur in some, and can be exacerbated by high doses and rapidity of infusion. Thrombotic events occur mainly in elderly patients with pre-existing risk factors receiving i.v. infusions, and have been associated with activated clotting factors existing as contaminants in some IgG products. Trace haemolysis is fairly common but is rarely severe, and can usually be attributed to anti-A and/or anti-B isohaemagglutinins in the IgG product. Research is under way to identify risk factors for these adverse events, and also ways to remove their causative components from the IgG product.

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