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Safety of intravenous immunoglobulin treatment

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SUMMARY In a prospective clinical and biochemical study of 16 patients treated with high doses of an immunoglobulin product that had been modified for intravenous use by mild pepsin treatment at pH 4 no evidence of hepatitis could be found. This contrasts with recent reports that intravenous immunoglobulin products can apparently transmit non-A, non-B hepatitis.

Intravenous immunoglobulin is increasingly being used as a substitution treatment for hypogammaglobulinaemia[1] and as an empirical treatment for several autoimmune disorders such as idiopathic thrombocytopenic purpura.[2] We report prospective biochemical and virological studies carried out as part of our investigation into the safety of intravenous immunoglobulin produced in Scotland.

Patients and methods

We studied 16 patients with idiopathic thrombocytopenic purpura and other immune disorders who were treated with intravenous immunoglobulin in the west of Scotland. They received a standard dose of 2 g/kg over five days. The immunoglobulin was manufactured by the Protein Fractionation Centre of the Scottish National Blood Transfusion Service. The product was prepared by cold ethanol precipitation followed by mild treatment with pepsin at pH 4. It was stabilised with maltose and freeze dried.

The immunoglobulin contained at least 97% intact monomers.[3] Each batch of immunoglobulin was prepared by fractionation of a plasma pool collected from around 10 000 blood donations. Patients were treated with material from 10 different batches, and four patients were treated with material from more than one batch.

Alanine transaminase was measured in serum samples from all patients before treatment and at one, two, three, and four weeks and two, three, and six months after treatment. Tests were carried out by an independent hospital laboratory.

Results

Results were within the normal range of 8–55 IU/l. Two patients, however, had raised alanine transaminase activity before treatment, presumably due to viral infection (both had clinically suspected infectious mononucleosis). Samples taken three weeks later, after treatment, gave normal results. A single sample drawn four weeks after treatment from a patient with autoimmune haemolytic anaemia (with a haemoglobin concentration of 50 g/l) gave an alanine transaminase activity of 60 IU/l. The patient was being treated at the time with cyclophosphamide, and the abnormality could have been induced by the drug.

All the specimens were negative for hepatitis B surface antigen by radioimmunoassay. One patient's specimen before treatment showed immunity to hepatitis B. Antibody to hepatitis B surface antigen (anti-HBs) attributable to the infusion was detected in all but one of the cases in samples collected one week after the start of treatment. The antibody remained detectable for three to seven weeks. Antibody levels were too low for accurate measurement or for measurement of half life.

Counterimmunoelectropheresis was used to detect a non-specific acute phase IgM antibody.[4] This test is known to give positive results in cases of acute viral hepatitis types A, B, and non-A, non-B as well as some Epstein-Barr and cytomegalovirus infections, whereas in hepatitis induced by drugs the test is negative. Out of 112 samples screened for "acute phase antibody" using counterimmunoelectropheresis, 10 samples from two patients were positive on initial screening. After absorption with polymerised human immunoglobulin samples failed to react on retesting by counterimmunoelectropheresis, suggesting that the initial reactions were due to the presence of rheumatoid factor or, less likely, Gm antibodies.

Discussion

No blood product should ever be prescribed without

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considering the possibility that infection may be transmitted. Preparations of immunoglobulin have an excellent safety record but the reason remains uncertain. The modified Cohn fractionation process may concentrate viruses in discard fractions while concentrating virus neutralising antibody in the immunoglobulin precipitate.[5] On the other hand, the reports by Lane,[6] Lever *et al*,[7] and Ochs *et al*[8] on the transmission of non-A, non-B hepatitis by slightly modified intravenous versions of well established safe intramuscular immunoglobulin products suggest that any change in manufacture of the immunoglobulin should be validated by clinical studies such as the one reported here. Of all the infections transmissible by plasma fractions, the commonest are hepatitis B and non-A, non-B hepatitis. We found no evidence that either was transmitted by this product despite the fact that all large plasma pools must contain at least one agent of non-A, non-B hepatitis, judging by experience with factor VIII.[9] Freedom from transmission of non-A, non-B hepatitis seems likely to be a function of the fractionation and finishing methods used. Fortunately, the antibody to HTLV-III has not been detectable in any of the batches of immunoglobulin (normal, hepatitis B, and cytomeglovirus) so far examined (B Cuthbertson, personal communication). This may change if HTLV-III becomes widespread among our donor population.

The data that we have presented suggest that Scottish intravenous immunoglobulin may safely be used for patients who may benefit. Although no absolute guarantee of safety can be given, the hazards of treatment with steroids, splenectomy, and immunosuppression are well known.

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