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# Adverse Effects of Intravenous Immunoglobulin Therapy

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## Contents



## Abstract

A growing body of literature documents that intravenous immunoglobulin prophylaxis and therapy is becoming applied to a steadily growing list of new indications. Some of these new indications have led to the use of intravenous immunoglobulin therapy in doctors offices, far from the hospital environment. Being stable products purified from blood or plasma donations, intravenous immunoglobulins must be considered as biological products in addition to their status as pharmaceutical products. This makes the study of adverse reactions reach beyond a mere drug safety surveillance programme into the realms of good manufacturing procedures guaranteeing not only intravenous tolerance but also sterility with regard to transfusion transmitted agents.

The initially perceived adverse effects, stemming from complement activating aggregated immunoglobulin G, had the effect of slowing down widespread introduction of intravenous immunoglobulin therapy in the late 1970s. These adverse effects have now been eliminated with amendment of the appropriate manufacturing steps. However, new adverse effects, such as hyperviscosity, aseptic men-

ingitis or renal insufficiency, have been observed which can be assigned to certain compounds of intravenous immunoglobulin, to administration regimens or to special patient characteristics.

Adverse effects can be divided into 3 types: immediate adverse effects (those that occur during the infusion, e.g. anaphylactoid reactions); delayed adverse effects (those that occur hours to days after initiation of the infusion, e.g. renal, pulmonary, dermatological adverse effects, hyperviscosity, aseptic meningitis, arthritis, cerebral infarction, haemolysis and leucopenia) and; late adverse effects (e.g. transmission of infectious agents).

We conclude from our analysis, that in general, intravenous immunoglobulin may be considered a well tolerated medical agent provided the indication for use is chosen carefully and use is monitored by a physician familiar with contraindications, risks, adverse effects and their appropriate management.

Year after year, the world's need for intravenous immunoglobulin infusions increases steadily and reached an estimated 30 000kg of immunoglobulin G prepared from human plasma donations in 1997. The aim of this review is to provide practising pharmacists and physicians with unbiased and evaluated information on the safety of intravenous immunoglobulin preparations used throughout the world. The body of knowledge on intravenous immunoglobulin preparations continues to grow, new preparations still emerge, new formulations are launched and old preparations are abandoned, reformulated or redefined. The information needs of those practising pharmacy and medicine continue to evolve, not least because of the expanding spectrum of clinical indications for intravenous immunoglobulin.

In this review, information on the adverse effects of intravenous immunoglobulin and their pathophysiology, treatment and measures used to avoid them is provided. Furthermore, general precautions, pharmacokinetic data and administration instructions for preparations will also be considered. Some information may be found in sources such as World Health Organization (WHO) publications,[1] the Council of Europe[2] and legislation,[3] others are available in official and standard publications, including those now found on the Internet. For the present review we performed a literature search of the Medline database. To give an idea about the prevalence of the different adverse effects, we will indicate whether their reports are based on studies involving many patients or on single case reports.

Adverse effects from the intravenous transfusion of immunoglobulin have been noticed ever since this route of administration was first attempted in the late 1970s.[4] At that time, the immunoglobulin preparations available differed considerably in properties and quality from those in use today, many of them containing aggregated immunoglobulin G, contaminating proteins, and/or low molecular weight polypeptides arising from the purifications steps. The large amount of intravenous immunoglobulin used up to now reflects an excellent safety record.

Nowadays, a proportion of the immunoglobulins manufactured is administered in the context of controlled clinical studies which are particularly attentive to problems of safety. However, recently, sales of intravenous immunoglobulin preparations to practising physicians who administer these preparations in their private practice have doubled. The safety issue forms an integral part of the evaluation of the results in most studies of clinical efficacy but because of the limited time frame of such types of studies,[5] long term safety data on transmission of infectious agents must be collected using retrospective procedures on the basis of the intravenous immunoglobulin producer and production lot linked to the individual patients. Not surprisingly, the findings thus far published on the adverse effects of intravenous immunoglobulin have focused primarily on the immediate and intermediate term

adverse effects, neglecting somewhat those manifestations which could eventually develop into serious problems in the long term follow up of patients. In fact, examples of medical treatments that turn out to be deleterious when their effects are evaluated months or even years after their administration, are well known.[6]

Toxicity of intravenous immunoglobulin could potentially arise: (i) from particular antibody specificities in intravenous immunoglobulin; (ii) as a nonspecific effect of increased immunoglobulin G levels; (iii) as an unintended consequence of the manufacturing process (impurities, stabilising agents, or chemically altered immunoglobulin in the final product); or, (iv) from infectious agents (table I). Various patient characteristics, depending on the mechanisms of toxicity involved, may increase the risk of an adverse event.

The literature reporting adverse reactions with intravenous immunoglobulin in clinical therapy alludes to incidence rates that vary widely from 1 to 81%.[8-10] Serious adverse effects with routine use occur for all indications with an incidence of less than 5%.[10] The majority of adverse reactions are mild, transient and self-limited and do not require discontinuation of therapy.[8] An increasing number of more serious reactions, however, are emerging with the use of higher doses and include renal failure, thromboembolic events (cardiac, cerebral, deep venous), hypotension, congestive heart failure and aseptic meningitis.[10] Most patients at risk for these adverse effects have an identifiable risk factor (see section 6) [table II].

There does appear to be a difference between immunoglobulin preparations produced by different manufacturers with respect to the overall incidence of adverse reactions. Some manufacturers remove immunoglobulin A from their preparations by immunoadsorption whereas in other preparations as much as 1mg of immunoglobulin A per gram of immunoglobulin G is still present possibly inducing adverse effects in immunoglobulin A deficient recipients upon repeat administration. For a long time pharmacovigilance studies were not required and only recently have some manufacturers started post marketing clinical surveillance of their product. In the prescribing information of some products the predicted incidence for adverse reactions varies between 1 and 16%. Different products should be given at different rates of infusion due to the presence of different stabilisers and differences in total protein content, pH, and particle count.

**Table I.** Components of intravenous immunoglobulin (Ig) preparations which may cause immediate adverse effects with proposed mechanisms of symptom generation[a]

| Component | Mechanism of adverse effect |
|---|---|
| IgG complexes (aggregates) | Activate classical pathway of complement |
| Ig fragments | Vasoactive properties |
| Incompletely dissolved lyophilisate | Clogging of tubing |
| Stabilisers, sugars | Renal adverse effects |
| Total protein load | Hyperviscosity |
| Albumin | Hyperviscosity |
| Temperature of solution infused | Critical in patients with cold agglutinin disease |
| Acute complement activation in agammaglobulinaemia patients | As little as a few dimers may activate complement and cause symptoms in such patients |
| IgA | Sensitised patients with anti-IgA form immune complexes with IgA in preparation |
| Low molecular weight polypeptides | Inflammatory reactions |
| Alloantibodies to blood type A/B | Extracorpuscular haemolytic anaemia |
| Infectious agents | Local and general inflammatory reactions to invasion of tissues by pathogenic micro-organisms that might contaminate plasma products |

a In a recent survey the manufacturers of 14 different polyvalent intravenous immunoglobulin preparations provided information on selection of donors, production processes, virus elimination capacity and contents and properties of the resulting products. The results have been published in table form elsewhere.[7]

Adverse effects from intravenous immunoglobulin therapy may be classified according to the mechanisms by which they arise or by the distinction between immediate and later effects. Most adverse effects are mild, transient and related to the speed of the infusion. These reactions usually oc-

cur within the first hour of the infusion. There is a large interpatient variability with respect to infusion speed tolerance. Prophylaxis with a nonsteroidal anti-inflammatory drug or an antihistamine is rarely needed (table II). If fever and hypertension occur at the end of the infusion or later, they may be related to pyrogen contamination of the product.

With 2-decades of experience with intravenous immunoglobulin, the list of reported adverse effects has grown and in this review we will comment on established and newly observed adverse effects. Some of these newly observed adverse effects are rare and the causal relationship to intravenous immunoglobulin not unequivocally established.

## 1. Immediate Adverse Effects

Immediate adverse effects (i.e. those arising during the infusion) usually arise from the triggering of an inflammatory response by constituents in the intravenous immunoglobulin preparation. Some of the components of intravenous immunoglobulin which have been implicated as causing specific adverse effects are shown in figure 1 and table I. The first intravenous immunoglobulin preparations used contained immunoglobulin G complexes due to the extreme stickiness of the immunoglobulins that leads to aggregation upon purification from the remainder of the plasma proteins (immunoglobulin G contains nonpolar groups), a problem that has since been resolved.

Modern preparations, although devoid of aggregated immunoglobulin G, may nevertheless cause immediate or anaphylactic reactions, although these are extremely rare. They may manifest as headache, flushing of the face, a feeling of tightness in the chest, dyspnoea, back pains, nausea, vomiting, diarrhoea and sometimes circulatory collapse.[4]

After 20 years of intravenous immunoglobulin use, headache probably remains the single most frequently reported mild, and transient immediate adverse effect.[8,11,12] Its prevalence is not dependent on the indication for intravenous immunoglobulin use (neurological versus non-neurological.[8] Headache was also the most frequent adverse effect occurring in 61% of patients in a series of 54 patients[13] and in 26% of another series of 88 patients[10] treated with high dose intravenous immu-

**Table II.** Signs and symptoms of adverse effects of intravenous immunoglobulin with proposed avoidance and treatment strategies

| Sign/symptom | Avoidance | Treatment |
|---|---|---|
| Nonspecific symptoms:[a] Pain (headache, backache), nausea, vomiting, diarrhoea, flushing, fever, chills, shaking, shortness of breath, tightness of chest, generalised tingling, hypotension, rashes | Administer nonsteroidal anti-inflammatory drugs and antihistamines prior to infusion | Stop or slow down infusion. General therapeutic handling according to prevailing symptom |
| Aseptic meningitis[b] | Slow infusion speed, avoid usage of intravenous immunoglobulin in patients with migraines | Analgesics |
| Cerebral infarction[c] | Do not use intravenous immunoglobulin in patients with advanced cerebral atherosclerosis and/or exsiccosis | Use antiplatelet agents |
| Renal failure[c] | Look for alternative treatment | Standard treatment of renal insufficiency according to severity |
| Hyperviscosity[c] | Try lower dosage, try less concentrated preparation | Infuse crystalloids |
| Myocardial infarction[c] | Do not prescribe to patients with recent history of coronary disease | Standard treatment of myocardial infarction |
| Haemolysis[c] | Manufacturer must absorb out high titered anti-A/B | Standard treatment of acute haemolysis |

a Prevalence up to 5%.
b Prevalence is highly dose dependent.
c Prevalence: rare (single case reports).

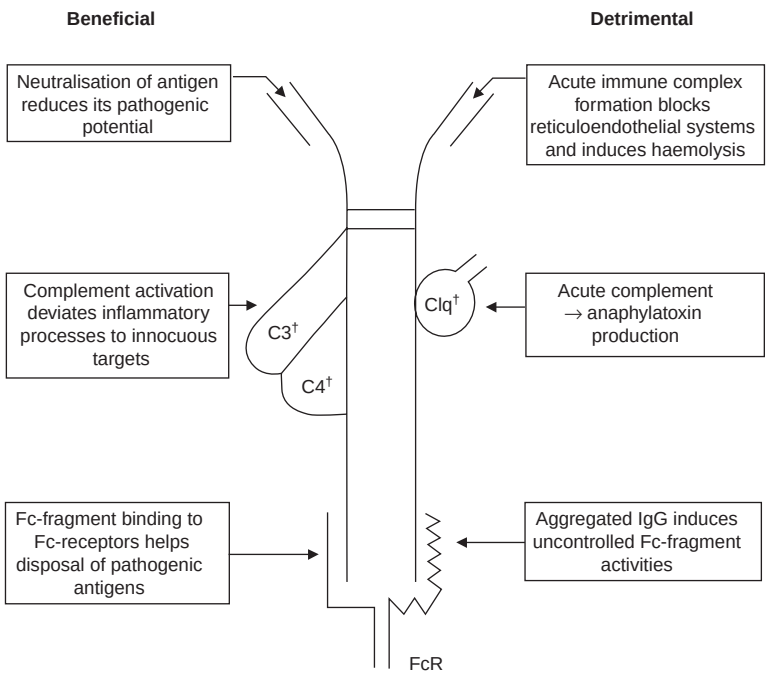


**Fig. 1.** How the beneficial effects of intravenous immunoglobulin may turn into adverse effects. The critical parts of the molecule in this respect are depicted. **Fc** = effector portion of IgG; **FcR** = Fc receptor; **IgG** = immunoglobulin G; † = C3, C4 and Clq are all major complement components.

noglobulin (2 g/kg). In contrast, headache was not reported in any of 76 patients treated for Guillain-Barré syndrome when a low dose was used.[14]

Dramatic reactions may occur almost exclusively in previously untreated agammaglobulinaemic patients with chronic infections. In such patients, intravenous immunoglobulin may lead to acute complement activation with the production of anaphylatoxins C3a and C5a.[15]

These, along with acutely formed antigen/antibody complexes,[16] may trigger mast cells and polymorphonuclear granulocytes to release histamine and other granular compounds.

With the exception of these relatively uncommon patients, the frequency of anaphylactoid reactions is now low. Mild reactions comprising fever, malaise, myalgia and headache occurring during or within hours of completing the infusion have been seen in 4% of 76 patients and in 4.6% of 130 patients treated for Guillain-Barré syndrome in prospective controlled trials.[14,17] These symptoms often respond to a reduction in the infusion rate.

The undesirable release of pro-inflammatory cytokines, such as tumour necrosis factor and other interleukins, may also take place[18] although, on the other hand, the modulatory role of intravenous immunoglobulin on these cytokines, in the context of particular therapeutic regimens is most appropriate.[19] Intravenous immunoglobulin may provide protection against these cytokines, which are involved in reactions against the transfusion of other blood products. The different donor pools and the diversity of production processes explain the variable and in some instances noticeable amounts of immunoglobulin A and interleukin-6 in certain preparations.[20] Furthermore, soluble human leucocyte antigen molecules and their ligands CD4 and CD8 may be present in varying amounts in some intravenous immunoglobulin preparations.[21]

While the recent intravenous immunoglobulin preparations, in conformity with WHO guidelines and US Food and Drug Authority (FDA) regulations, are devoid of many of the contaminants noted above, they still may contain varying amounts of contaminating immunoglobulin A,[22] which can elicit anti-immunoglobulin A antibodies in totally immunoglobulin A-deficient recipients, whereby anaphylactic reactions in some immunoglobulin A deficient patients might be related to immunoglobulin E formation against immunoglobulin A. This situation has lead to immediate or anaphylactic reactions since the injected immunoglobulin A will form macromolecular complexes with anti-immunoglobulin A of the recipient. Selective immunoglobulin A deficiency is one of the most common, usually asymptomatic immunodeficiencies (the prevalence is about 1 in 1000) and may be associated with systemic autoimmune disorders. The risk of intravenous immunoglobulin reaction in a selective immunoglobulin A deficient patient is unknown given the frequency of immunoglobulin A-deficiency as opposed to the paucity of diagnosed immunoglobulin A/anti-immunoglobulin A reactions. Anti-immunoglobulin A antibodies are present in about 30% of individuals with selective immunoglobulin A deficiency, but do not necessarily predict adverse reactions.[23] In patients who do not have hypogammaglobulinaemia or disorders associated with immunoglobulin A deficiency (such as ataxia telangiectasia), screening for immunoglobulin A deficiency prior to intravenous immunoglobulin is probably not justified.[24]

Low molecular weight polypeptides and compounds activating the plasminogen pro-activator and hence the fibrinolysis system, may also produce adverse effects. Finally, a simple allergic reaction to foreign immunoglobulin G with a consequent increase in immunoglobulin E may be possible. Some of the reactions, in our experience will wane if the infusion is stopped or, in some cases, after the injection of corticosteroids or antihistamines. Intravenous immunoglobulin prepared from pooled plasma unavoidably contains alloantibodies other than anti-ABO (see section 2.8). However, the concentration of any particular alloantibody is probably too low to be pathogenic in most cases. Some of the rare idiosyncratic reactions to intravenous immunoglobulin, including alopecia,[25] aseptic meningitis,[26] and uveitis[27] have been linked to alloantibodies.

Bacterial contamination of intravenous immunoglobulin preparation has not been reported because it is prevented by sterile handling upon infusion.

Immediate adverse effects may be avoided by awareness or may be attenuated if treated appropriately (table II). Thus, as with any infusion that causes a reaction, the administration should be stopped immediately. The infusion bottle should then be preserved for further examination and a sample of the recipients plasma taken for laboratory examination. Such samples can also be sent to the manufacturer for extended examination and comparison with the reference split sample hold back by the producer.

As a rule, the precise reason for the adverse effect should be determined before the treatment is resumed. In most cases, however, the reasons will remain obscure. In pressing situations we have successfully used intravenous corticosteroid injections prior to intravenous immunoglobulin administration (table I); the case history of a 5-year-old boy in whom intravenous hydrocortisone was successfully used has been described previously.[28]

## 2. Delayed Adverse Effects

### 2.1 Renal Adverse effects

The possibility for renal adverse effects was discovered in our hospital when we treated a patient with haemorrhagic diathesis due to the presence of acquired clotting factor VIII inhibitor.[29] The patient was treated earlier for renal failure requiring dialysis for 5 months. On admission, his plasma creatinine level was 315 μmol/L, rising to 541 μmol/L after 5 days of intravenous immunoglobulin therapy at a dosage of 0.4 g/kg bodyweight. He became oliguric, but normal renal function returned in a week with supportive measures only, and the

haemorrhagic syndrome improved. At the same time, Schifferli and colleagues,[29] had initiated an open trial of intravenous immunoglobulin treatment at the same dosage regimen in nephrotic patients with glomerulonephritis; their first 6 patients showed a transient rise in plasma creatinine levels. It was concluded from these observations that an increase in plasma creatinine levels in intravenous immunoglobulin–treated patients with pre-existing renal disease may occur without inevitably leading to irreversible renal damage.

The study of Schifferli et al.[29] sparked interest and focused attention on the adverse effects caused by intravenous immunoglobulin in definite patient groups. In fact, this observation was confirmed by Tan et al.,[30] who reported renal adverse effects in a patient with chronic inflammatory demyelinating polyneuropathy. The patient experienced an increase in creatinine levels from 140 μmol/L before treatment with intravenous immunoglobulin to 480 μmol/L after treatment. Renal biopsy showed swelling and vacuolisation of the proximal tubular epithelial cytoplasma typical of a hyperosmolar insult, and no antigen-antibody complex deposits were found. To further underline the transient nature of the renal adverse effects of intravenous immunoglobulin, the patient tolerated subsequent infusions of a decreased intravenous immunoglobulin dose given at a slower rate without experiencing problems.

In the meantime, about 40 cases of acute renal failure associated with intravenous immunoglobulin therapy have been reported,[31] about half of the patients had pre-existing renal disease. Interestingly, and at variance with the experience of Tan et al.,[30] and experience with the occurrence of aseptic meningitis (see section 2.5), the occurrence of renal failure has remained generally independent of the concentration of the intravenous immunoglobulin solution and the rate of infusion. The major and apparently reversible histological finding in most cases is swelling and vacuolisation of proximal tubular cells with preservation of brush borders.

There is no uniform explanation for these histological renal abnormalities associated with intravenous immunoglobulin administration. An adverse effect of carbohydrates added to stabilise intravenous immunoglobulin is the most frequently cited cause. Tan et al.[30] proposed that 1 nephrotoxic factor in intravenous immunoglobulin is sucrose, a stabilising agent for some intravenous immunoglobulin products.[30] Therefore, it is important to remain cautious when using high dose intravenous immunoglobulin in patients with severe or even moderate renal failure.

Do all intravenous immunoglobulin products have a similar risk of nephrotoxicity? The currently available products contain sucrose, glucose, sorbitol or maltose as a stabilising agent in concentrations ranging from 2 to 10%;[20] renal toxicity from high solute loads is not unique to sucrose. Similar vacuolar changes in renal tubules have been described after mannitol infusions. Even in patients with mild renal impairment, and with an indication requiring only low doses of intravenous immunoglobulin, increased vigilance and monitoring of renal function (in some cases even after therapy) should enter the standard clinical management of patients receiving intravenous immunoglobulin.[32] On the basis of this information it is advised that a normal renal function must be ascertained prior of initiation of intravenous immunoglobulin therapy.

### 2.2 Hyperviscosity

An elevated blood viscosity impeding capillary blood flow is a well known consequence of polyclonal gammopathy and causes leading symptoms, such as headache, visual blurring and bleeding, in patients with paraproteinaemia.[33] Mechanisms by which intravenous immunoglobulin may increase serum viscosity are related to immunoglobulin G concentrations >18 g/L in the presence of normal and/or elevated immunoglobulin M and A concentrations, but may also involve immune complex formation and immunoglobulin aggregates.[34-36] Therefore, symptoms of hyperviscosity may emerge upon infusion of intravenous immunoglobulin

especially when infused into an already hyperviscous blood stream or in patients with arteriolosclerosis and poor regulatory capacity for vessel tone. Thus, headache, fatigue, blurred vision and retinal abnormalities have been reported in patients receiving intravenous immunoglobulin for HIV infection.[34] A 70-year-old woman was referred to our hospital for post-transfusion thrombocytopenia and was treated with intravenous immunoglobulin, 0.4 g/kg bodyweight for 5 consecutive days; she died on the fifth day of this course of treatment from a myocardial infarction.[35] Necropsy revealed severe coronary atherosclerosis without visible thrombotic occlusion and our colleagues found a substantial increase in plasma viscosity in this patient.[35]

Although frank thromboembolic complications such as myocardial or cerebral infarction, deep venous thrombosis or pulmonary embolism are rare (the incidence is 3%),[37-41] a considerable increase of serum viscosity can be measured in some patients following intravenous immunoglobulin infusion especially when the agent is administered at high doses and at a high rate.[35] With pre-existing conditions such as paraproteinaemia, serum viscosity may rise above 2 or 3 centipoise and become symptomatic.

From such studies, we and other authors,[35-38,42] have come to the conclusion that elderly patients with low cardiac output and/or atherosclerotic stenosis and hence with limited microcirculatory blood flow in certain areas, may be particularly prone to adverse effects from increased plasma viscosity after intravenous immunoglobulin administration. We have thus begun to carry out electrocardiographic check ups before starting intravenous immunoglobulin therapy in elderly patients with a suspected or overt cardiovascular history and to use methods of treatment that lowers viscosity combined with reduced infusion rates in patients at risk (table II). In addition to pre-existing vascular disease, further risk groups for development of symptomatic hyperviscosity are patients with cryoglobulinaemia, monoclonal gammopathies and high lipoprotein levels.[37] In such patients, serum viscosity should be determined before they receive intravenous immunoglobulin.

### 2.3 Pulmonary Adverse Effects

The pulmonary interstitial space is a well known site for allergic reactions and due to the relatively low content of structural collagenous fibres it is prone to oedema. One therefore has to distinguish between pulmonary allergic/anaphylactic,[13] and pulmonary oedematous complications the latter being caused by volume overload in patients with circulatory insufficiency or pre-existing pulmonary capillary leakage.[43] With modern intravenous immunoglobulin preparations, pulmonary adverse effects are virtually nonexistent.

### 2.4 Dermatological Adverse Effects

A transient rash, urticarial or maculopapular, has been observed in up to 6% of treated patients.[10] More chronic cutaneous adverse effects have emerged very recently but proof of cause-effect relationship is difficult to establish and the prevalence is at the single case report level.[44] A lichenoid cutaneous eruption after administration of intravenous immunoglobulin appeared upon completion of a 70g infusion of 'Gamimune N' administered over 3.5 hours on 2 consecutive days for Sjögren syndrome in a 73-year-old man.[45] While the Sjögren syndrome was refractory to intravenous immunoglobulin, a pruritic papular eruption developed on the trunk and upper extremities.[45] Immunofluorescence revealed nonspecific fibrinogen deposition along with lymphocytic infiltration. Eczema, erythema multiforme, purpuric erythema and alopecia are further dermatological disorders that have been ascribed to intravenous immunoglobulin use,[10,45-48] but the mechanism for these is unknown.

### 2.5 Aseptic Meningitis

Headache is reported at an incidence that varies from 4.7 to 80% and seems to be dose and rate dependent.[8] Most instances are mild, transient and interruption of therapy is not required. In chil-

dren treated for acute idiopathic thrombocytopenic purpura, headache occurred in 34% in 1 study.[49] Cases of aseptic meningitis requiring discontinuation of therapy with intravenous immunoglobulin have been recently reported[10,14,50] and strategies to avoid neurological adverse effects have also been developed recently.[51,52]

In a study conducted by Sekul et al.[14], of 54 patients treated for neuromuscular diseases (inflammatory myopathies, paraproteinaemic neuropathies, amyotrophic lateral sclerosis, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy) an alarmingly high number (6/54; 11%) developed severe symptoms. All 6 patients had severe headache often with acute onset, nuchal rigidity, drowsiness or lethargy, fever, photophobia, painful eye movements, nausea and vomiting. CSF findings showed polymorphonuclear pleocytosis (up to 1200 cells/μl) and increased protein content (up to 1 g/L), glucose level was normal but cultures for bacteria remained sterile. Symptoms were always transient and lasted for 3 to 5 days. Aseptic meningitis may closely mimic bacterial meningitis. In this study, patients with a history of migraine were particularly prone to developing recurrent aseptic meningitis regardless of the commercial preparation used, the daily dose, or of the infusion rate, and therefore should not receive intravenous immunoglobulin at all if possible. Simultaneous treatment with corticosteroids did not have any protective effect. Among the remaining 48 patients, another 56% reported mild, transient headache.

The exact mechanisms of aseptic meningitis are not clear. An allergic hypersensitivity meningeal reaction induced by entrance of the allogeneic immunoglobulin into the intrathecal compartment seems most likely. The CSF protein content is markedly increased and the increase parallels the intravenous immunoglobulin dose administered.[14] The allogeneic immunoglobulin G does cross the blood-brain barrier and has been verified in the CSF. Use of muromonab-CD3 (OKT3) may have a similar adverse effect. Experimental studies have shown that the muromonab-CD3 reaction is caused by a cytokine release syndrome following transient T cell activation. The same mechanism has been postulated for this adverse effect following intravenous immunoglobulin.[49] The work of Scribner and co-workers[50] reviewed another 36 patients from the literature who developed aseptic meningitis following intravenous immunoglobulin treatment with different commercial preparations and for various neurological and non-neurological indications.

The frequency of this adverse effect is not established but seems related to the dose used. In the study of Sekul et al.[14] with 54 patients, 6 developed aseptic miningitis within 24 hours of completion of infusions. Symptoms, lasting 3 to 5 days, included severe headache, meningismus, photophobia and fever. The dosage was high (2 g/kg) and administered in a short time (24 hours) and for treatment of idiopathic thrombocytopenic purpura, dosages of 1 g/kg given over 24 hours were administered.[49] Two studies analysing the efficacy of intravenous immunoglobulin in patients with Guillain-Barré syndrome did not find any case of aseptic meningitis in 74 and 127 patients treated.[14,17] In both studies the dosage of intravenous immunoglobulin administered was 0.4 g/kg given over 24 hours. Thus, until further observations focusing on aseptic meningitis become available, we may state that aseptic meningitis remains a rare adverse effect of intravenous immunoglobulin therapy, the occurrence of which is clustered in patients with a history of migraine and only when high dosages (1 g/kg given over 24 hours or more) are infused in short periods of time.

### 2.6 Arthritis

Arthritis following administration of intravenous immunoglobulin seems to be exceptionally rare (single case report prevalence) and is probably explained by the formation of specific antibody-antigen immune complex aggregates.[16,53] In patients who experienced this adverse effect symptoms included severe joint pains especially involving knees and wrists, but these symptoms were transient and of short duration (10 days).

### 2.7 Cerebral Infarction

In patients experiencing adverse renal effects the osmolality of plasma may be responsible for thrombogenesis secondary to hyperviscosity. Case reports in single patients of both cerebral infarction and myocardial infarction have been reported especially in older patients with cerebrovascular or cardiac disease or vascular risk factors.[35,37-40] Plasma viscosity may rise by as much as 2 to 3 centipoise. It is therefore not recommended to use products with an osmolality greater than 350 osmol in older patients. From the few patients who have experienced a cerebral infarction, it is not clear whether the stroke was a consequence of altered haemorheology[35] due to increased blood viscosity or whether it was a consequence of altered levels of activity of clotting factors or platelet aggregability.

### 2.8 Haemolysis

It has been known for a long time that stable plasma derivatives from human blood can contain anti-blood group antibodies – more precisely, anti-A/B immunoglobulin G directed at the histo blood group ABO system antigens. Buchs and Nydegger[54] and others[55-57] found varying amounts of such antibodies in intravenous immunoglobulin preparations.

The issue might possibly gain a new dimension if intravenous immunoglobulin M preparations become of interest to clinicians who may prefer it to intravenous immunoglobulin G for certain indications. In fact, immunoglobulin M is efficient in modulating complement activation and represents a clinical interest based on *in vitro* experimental evidence when it comes to modulating primary immune response. The first preparation available for use that is enriched with immunoglobulin M, 'Pentaglobin', is subjected to strict immunoabsorption for removal of anti-A/B immunoglobulin M for this isotype is known to comprise the bulk of the haemolysing isoagglutinins.[58] Thus, we have used an ELISA-technique to estimate the correlation between the amount of anti-A blood group antibodies and their respective complement activating capacity. For this purpose, the amount of the first subcomponent of complement (C1q) fixed to ELISA plates by anti-A and the haemolytic isoagglutinin activities were compared in 69 0-type serum samples. 52 out of the 69 (i.e. 75%) 0-type sera showed haemolytic antibodies and/or C1q binding. Because binding of C1q was also seen with anti-A immunoglobulin G, plasma pools used to produce intravenous immunoglobulin contain complement activating anti-A/B antibodies which should be removed.

Some manufacturers remove these antibodies by affinity chromatography, but many preparations still contain substantial amounts of anti-A/B immunoglobulin G. For example we have found 1 molecule of specific-anti-A per 4.1 to $31 \times 10^5$ of total immunoglobulin G molecules.[59] In 7 different preparations tested, anti-B immunoglobulin G levels varied from 0.44 to 13.4 μg/g of total immunoglobulin G. It is not so much the quantity, but rather the capacity of such antibodies to act as haemolysins through complement activation, that determines the ability of anti-A/B to induce a direct antiglobulin reaction in the recipient and/or induce haemolysis. 'Sandoglobulin' is the intravenous immunoglobulin preparation that is most often used in our clinic, and anaemia resulting from contamination with anti-A/B in this preparation has never been a perceived problem.

### 2.9 Leucopenia

Neutropenia has been observed occasionally in a few patients (single case report prevalence),[60] a finding, that when it occurred in our patients, has so far never been ascribed to intravenous immunoglobulin but rather to the patient's underlying disease. The suggestion made earlier in this decade, e.g. that the white cell count should be carefully monitored in patients receiving intravenous immunoglobulin,[60] turns out to be exaggerated since this drop of white blood cells is always transient[10] and in most cases asymptomatic.

## 3. Late Adverse Effects: Transmission of Infectious Agents

The long term safety of intravenous immunoglobulin preparations is excellent. Until recently, most physicians believed that the administration of intravenous immunoglobulin was associated with no risk of infectious transmissions (notably viral). With respect to HIV infection, no documented instance of transmission by intravenous immunoglobulin has ever been reported. This includes the intravenous immunoglobulin preparations that were manufactured before serological tests for HIV were available, when the virus was present in plasma pools and was found to be transmitted by clotting factor concentrates. This suggests that HIV is inactivated or excluded in the manufacturing process and studies of plasma 'spiked' with HIV and then subjected to alcohol fractionation confirm this.[61,62] Any risk of HIV transmission, if it existed, has been presumably further reduced by exclusion of HIV-seropositive plasma since 1985.

Further viruses of concern for transmission are hepatitis A, hepatitis B, hepatitis C and parvovirus B-19 (P19). Originally it was thought that intravenous immunoglobulin was entirely safe with respect to transmission of these infectious agents. This assumption is questioned now, with an estimated 450 patients worldwide known to have contracted hepatitis C infection from intravenous immunoglobulin preparations.[63-66] Parvovirus, a non-enveloped virus may have been responsible for infecting 1 recipient,[66] but generally, P19 infection is rather a reason to use,[67] rather than avoid intravenous immunoglobulin. There is no evidence to suggest that there is transmission of hepatitis A or B.

Stringent criteria for licensing have meanwhile been introduced worldwide including testing single plasma units contributing to pools as well as final preparations by polymerase chain reaction. Transmission of hepatitis C virus occurred with 1 type of intravenous immunoglobulin preparation, namely a preparation that was processed using ion-exchange chromatography. This technique purifies immunoglobulin G to a high degree but fails to partition hepatitis C viral particles away from the immunoglobulin G fraction. This issue has been extensively reviewed elsewhere.[68]

The exceptionally high safety of human immunoglobulins is not simply due to the exclusion of hepatitis B surface antigen or anti-HIV and anti–hepatitis C positive blood and plasma donations. It also depends on the following factors: (i) neutralisation of infectious viruses by specific antibodies present in the plasma pools from which the immunoglobulins are isolated; and (ii) inactivation and/or elimination of the viruses during the manufacturing process. Sound manufacturing procedures require additional virus inactivation steps such as solvent/detergent, filtration, pH 4/pepsin inactivation, polyethylene glycol precipitation and/or pasteurisation (10-hour treatment of the aqueous solutions at 60°C). It is the manufacturer's responsibility to apply these procedures under adherence to good manufacturing practice standards without compromising the efficacy of the preparation. It is generally believed that intravenous immunoglobulin is now free of viral transmission, but this is not unequivocal.[69]

We are currently going through a period where manufacturers are developing a host of new and potentially even more efficacious intravenous immunoglobulin G, M and A products incorporating 1 or more of the above mentioned virucidal steps. There is, however, no 100% safe procedure. The manufacturers employ different steps to ensure viral elimination and thus the different products also provide different degrees of safety.

### 3.1 Prion Diseases

The rare disorder Creutzfeldt-Jacob Disease (CJD) belongs to the group of transmissible subacute spongiform encephalopathies. The unconventional transmissible agents are supposed to be proteinaceous infectious particles, i.e. prions, which represent a protease-resistant modification of a membrane protein on the surface of nerve cells.

All transmitted cases of CJD so far are iatrogenic transmissions attributed to growth hormone

extracted from cadavers harbouring CJD, use of intracerebral electrodes, corneal transplants and dura mater transplantations from pooled products. There is no evidence, so far, that blood products are capable of transmitting CJD, although such transmission has been sought for actively with targeted postmarketing surveillance. When donors develop CJD years after they have provided a plasma donation has been used to prepare highly pooled stable products, such as clotting factor concentrates or intravenous immunoglobulin, manufacturers of plasma products are required to initiate the recall of production lots from the market. Thus, an estimate made in 1998 indicated that the American Red Cross had recalled plasma products worth more than US$100 million and the Central Laboratory of the Swiss Red Cross, producer of 'Sandoglobulin', has withdrawn considerable amounts of the product from the American market in this case stemming from American plasma pools as part of its foreign plasma fractionation programmes.

The US FDA was somewhat more strict to encourage recalls than the European Agency for the Evaluation of Medicinal Products (EMEA) which has stated that the scientific basis for product recalls to be implemented is lacking (Council of Europe 1998). The British government (UK Committee on Safety of Medicine) has allowed the importation of plasma for fractionation from abroad since some of the UK plasma-derived licensed blood products could have their licences withdrawn, as long as satisfactory alternatives are available.[70]

Until recently, there have been no experimental models available to allow the transmission of CJD by infected material to be studied. It has been recently concluded that differentiated B lymphocytes are crucial for neuroinvasion by scrapie since these cells are a limiting factor in the development of scrapie after peripheral inoculation.[71] Leucocyte depletion is now being considered to eliminate risky B lymphocytes in cellular blood products, the stable plasma-pool derived products do not carry this risk factor. Nevertheless, Maring et al.[72] have recently initiated studies by which the homogenised brain of scrapie infected hamsters was used to spike an intravenous immunoglobulin preparation. They observed that the infective spike was recovered in alcohol/cold plasma fractions not associated with the final intravenous immunoglobulin product.

Until more solid data in this difficult field have accumulated, we should be grateful that regulatory agencies with the assistance of a number of public advisory committees, have accepted far reaching decisions.[73] In the US, the shortages of intravenous immunoglobulin caused by extensive recalls has already meant that there is insufficient replacement therapy for patients in urgent need of immunoglobulin G replacement therapy to treat their humoral immunodeficiency.

## 4. Clinical Implications of Adverse Effects

For almost any adverse event that occurs during or after intravenous immunoglobulin therapy there are either known risk factors with respect of patient characteristics, or there is a significant influence of dose or rate of infusion. In terms of daily practice management this means that appropriate patient selection and use of the appropriate treatment schedules are important to reduce adverse effects. It is mandatory that for each patient a thorough history and physical examination is performed by a physician who is familiar with intravenous immunoglobulin indications, adverse events and their risk factors. Furthermore, infusions should be monitored since damage caused by unexpected (allergic/-anaphylactic) adverse events can be limited if these are recognised early on and adequately treated. Home infusions or use in indications/applications by physicians who are not familiar with intravenous immunoglobulin may do a bad service to a treatment modality otherwise with a good safety record.

According to several studies adverse events lead to the interruption of therapy in up to 16% of patients and permanent discontinuation in 7%.[10] It is self-evident that patients must be provided with the appropriate information regarding the possibil-

ity of complications. Individualisation of treatment to lessen the occurrence of adverse effects and adjusting rate and concentration accordingly is the consequence of an optimal management.

## 5. Risk/Benefit Ratio for Intravenous Immunoglobulin Treatment

Indications for intravenous immunoglobulin therapy should be strictly limited to those where controlled studies have shown a proven benefit unless the intravenous immunoglobulin is being used within a study protocol. Controlled studies have demonstrated benefit in the following indications: idiopathic thrombocytopenic purpura, Kawasaki disease,[74] humoral immunodeficiency, pure red cell aplasia, dermatomyositis, multiple sclerosis, Guillain Barré syndrome, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, Lambert Eaton syndrome and myasthenic syndrome. Intravenous immunoglobulin is most probably efficacious in the following indications, but controlled studies have not been performed so far: paraproteinaemic neuropathies (immunoglobulin G and immunoglobulin A), myasthenia gravis, some forms of lupus erythematosus, polymyositis and septic syndrome.

With such a patient selection and taking into consideration known risk factors with respect to patient characteristics especially when determining the treatment schedule, benefit is much higher than risk.

## 6. Procedures to Reduce Adverse Effects of Intravenous Immunoglobulin

The most important factors that determine the prevalence of adverse events and how they can be modified to reduce adverse effects are as follows.

1. Preparation used. The preparation should be changed if allergic adverse events occur.

2. Total dose applied. The dose should be reduced if, for example, hyperviscosity is the mechanism behind the adverse effect.

3. Infusion rate. The infusion speed can be reduced if, for example, the patient is experiencing a headache.

4. Patient conditions. Patients with a history of migraine can develop aseptic meningitis therefore the dose and rate of infusion should be reduced or avoided. Older patients and patients with a history of cardiac and/or cerebrovascular disease can develop hyperviscosity therefore the dose and rate of infusion should be reduced, blood viscosity should be determined and electrocardiogram performed. Patients with paraproteinaemia and high lipoprotein concentrations must be followed closely if they need intravenous immunoglobulin therapy. In patients with immunoglobulin A deficiency anaphylaxis can occur so it is vital to use a use preparation that is free of immunoglobulin A. For patients with chronic infections serum electrophoresis should be performed to check the patient's immunoglobulin profile. In patients with renal insufficiency creatinine level and creatinine clearance should be determined.

5. Infusion surveillance. The patient should be kept under surveillance during the infusion to monitor the dose, monitor the infusion rate, observe for allergic events, measure blood pressure and if necessary the infusion should be stopped or slowed down or the total dose could be reduced. The bottle should be preserved for postmarketing analysis.

6. Individualise treatment schedule. (See also table II).

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