Immunoglobulins and Their Use in Children

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Abstract

Immunoglobulin preparations are one of the products of the human plasma fractionation, where the plasma is obtained, in accordance with WHO guidelines from at least 1,000 donors. These preparations contain all IgG subclasses with various antigen characteristics. In clinical practice these drugs are used as replacement therapy in patients with primary and secondary immunodeficiencies as well as immunomodulatory therapy in many autoimmune diseases and systemic inflammatory diseases. Here we present characteristics of i.v. polyvalent, human immunoglobulin preparations available on the Polish market and the possibilities of their use in clinical practice, in children with hematological diseases. Considering the very low consumption of immunoglobulin preparations in our country as compared to other European countries, we would like to draw the attention of medical professionals, especially pediatricians and haematologists, to the benefits that stem from the use of these drugs in the therapy of children with haematological diseases. Our work will also facilitate the choice of an optimal polyvalent human immunoglobulin preparation for a particular patient (Adv Clin Exp Med 2015, 24, 1, 153–159).

Key words: i.v. immunoglobulin preparations, immune thrombocytopenic purpura, children.

Aim

As there are so many different iv immunoglobulin preparations on the market, we have decided to present their characteristics and clinical use. We would also like to point out the differences in the manufacturing process which, by influencing physico-chemical end-parameters of particular products, may affect therapeutic efficacy within this, only apparently homogenous, group of drugs.

Manufacturing of iv Immunoglobulin Preparations

As we have already pointed out, immunoglobulins are one of the products of human plasma fractionation. Industrially there are two similar methods used in human plasma fractionation:
the Cohn-Oncley fractionation process, the Kastler-Nitschmann method.

During fractionation plasma is submitted to sequential precipitation and split into fractions using variable concentrations of ethyl alcohol, pH, temperature and ion exchangers [2, 3]. Out of each fraction, after discarding impurities, valuable medications are produced: albumins, clotting factors and, of course, immunoglobulins. An exemplary Cohn-Oncley fractionation process is presented on graph 1 [4]:

The Kistler-Nitschmann method is similar. It is quicker (one less incubation in alcohol) but does not lead to IgA elimination. That is why, during further immunoglobulin processing, it is necessary to use chromatography to isolate this fraction. Final, ready-to-use IgG should contain no less than 90% protein, without considering additional proteins used e.g. to stabilize the final product [5].

Techniques Used to Protect Immunoglobulins from Pathogens

The process of immunoglobulin manufacturing may sometimes raise doubts regarding the safety of these types of products, especially because of the risk of transmitting potential infectious particles or prion infections [6–8]. Analyzing the data in literature, these reservations seem totally unfounded. Statistical data confirms that immunoglobulins available today are safe. In this class of drugs there have been no reports of the transmission of blood-borne infections for over 30 years.

An unquestionable influence on the development of safety procedures in blood derivatives, including iv immunoglobulins, was the discovery of infections in haemophilia patients who were taking clotting factor at the beginning of the 1980s. Insufficient safety procedures led to HIV infections in many of these patients. An ‘HIV epidemic’ in the haemophiliac population gave an impulse for the production of recombinant clotting factors and for inventing new procedures ensuring the safety of plasma derivatives [9].

The safety of IVIG is guaranteed by a continuous technological progress [10] – refining methods of inactivation of both encapsulated and non-encapsulated pathogens, elimination of pathological PrPSc prions and new filtration methods [11]. These can also eliminate such ‘emerging pathogens’ as the West Nile virus, Ebola or avian flu, as well as of non-encapsulated viruses and prions [12–15].

It has to be stressed that all iv immunoglobulin preparations available on the Polish market exceed the requirements regarding pathogen
Immunoglobulins and Children

Stabilizers

Preserving immunoglobulin G in its native form is a challenge for every manufacturer. It is one of the reasons for adding external substances to prevent the drug from aggregation. Most often sugars or amino-acids are used as stabilizers. Sadly, there are no stabilizers that are not potentially linked with adverse effects. One of the most serious complications after immunoglobulin treatment is the risk of kidney failure linked with the presence of sucrose in some of the IgG [19, 20].

Depending on the substance added as a stabilizer, we may expect particular adverse effects enumerated in Table 1.

Table 1. Stabilizers and their most frequent adverse effects

<table>
<thead>
<tr>
<th>Stabilizer</th>
<th>Most frequent adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycine</td>
<td>nausea, vomiting, excessive sweating, headache, fever</td>
</tr>
<tr>
<td>Maltose</td>
<td>blood glucose monitoring systems falsely recognize maltose as glucose, distorting glucose readings</td>
</tr>
<tr>
<td>L-proline</td>
<td>proline-containing IgG are contraindicated in patients with hyperprolinemia</td>
</tr>
<tr>
<td>Sucrose</td>
<td>kidney damage</td>
</tr>
<tr>
<td>Sorbitol</td>
<td>sorbitol-containing IgG should not be used in diabetics and patients with fructose intolerance (fructose is one of sorbitol’s metabolites)</td>
</tr>
</tbody>
</table>

IgA Content and the Risk of an Anaphylactic Reaction

For years the content of type A immunoglobulin in the i.v. immunoglobulin preparations has been synonymous with potential risk of anaphylactic reactions. That is why all immunoglobulin manufacturers strive for decreasing IgA content in the final product.

Thirty years ago intravenous immunoglobulin preparations with increased IgA content were popular and used to treat viral infections. Studies conducted at that time showed no sign of specific anti-IgA antibodies in the sera of patients undergoing such therapy. No cases of anaphylactic reactions were reported [21]. Anaphylactic reactions after the administration of immunoglobulins rarely resulted in a lack of recommendation for routine screening of patients for the presence of anti-IgA antigens before IVIG administration [22]. It seems
that the administration of intravenous IgG is safe, even in patients with IgA deficiencies [23].

Another way to reduce the risk of anaphylactic reactions, apart from reducing IgA content, is to modify an immunoglobulin preparation in such a way as to make it suitable for subcutaneous delivery. After administering subcutaneous IgG preparations, inconsiderable resorption into the circulation and a long release time leads to a smaller release of inflammatory mediators [24]. Moreover, this route of administration is safe even in patients with confirmed anti-IgA antibodies [25, 26].

Table 2 shows the characteristics of several immunoglobulin preparations presently available in Poland. We have presented only some of the features, those that in our opinion are most important when choosing the best preparation for a particular patient.

**Immunoglobulin**

**Mechanism of Action and Clinical Use**

The mechanism of immunoglobulin effect on the immune system is varied and still remains a topic of research. Suggested regulatory mechanisms of immunoglobulin action include:

- stimulating production of some of the cytokines and their antagonists [27–30];
- stimulating B & T lymphocyte apoptosis by activating Fas receptors [28, 31];
- inhibiting differentiation and maturation of dendritic cells [32];
- increasing catabolism of IgG [28, 29];
- modulating expression and function of an Fc fragment through FcγR receptors [29, 30, 33];
- blocking the binding of T lymphocytes with superantigens [34].

A modulatory factor for immunoglobulins in the immune system is widely used in therapy, especially in the treatment of autoimmune and inflammatory diseases. The following blood disorders are significant: immune thrombocytopenic purpura (ITP), autoimmune haemolytic anemia (AIHA) and pure red cell aplasia (PRCA).

The fact that human immunoglobulin intravenous preparations are safe, have few adverse effects and are usually well tolerated makes them particularly suitable for use in children with autoimmune cytopenias. These preparations have an important role in therapy, especially in the treatment of newborns and babies.

Thus, IVIG are clearly among the best clinically tested drugs in one of the most frequently diagnosed childhood diatheses – the immune thrombocytopenic purpura (ITP) [35–38]. Here the mechanism of action is based mainly on Fc phagocyte receptor saturation and neutralization of anti-platelet antibodies by anti-idiotypic antibodies. Some data suggests that TGFβ present in the human IVIG solutions affects the auto-aggression process, and that there are anti-cytokine antibodies against interleukin-1 (IL-1) and interleukin-6 (IL-6) (essential for the production of anti-platelet antibodies). The therapeutic efficacy of immunoglobulin preparations in children with ITP is indubitable and the treatment response is similar to that achieved with corticosteroids, with shorter treatment duration [39]. Typical dosing regimen for IgG consist of a dose of 0.4 g/kg for 5 days or of a dose of 1 g/kg for 2 days [40]. According to some authors, a shorter time of administration and larger doses of IgG result in faster increase in platelet number, even within 24 h.

IVIG are also the drug of choice in fetal and neonatal alloimmune thrombocytopenia. This disease develops when the mother produces antibodies against platelet antigen (most frequently the HPA-1a) inherited by the child from the father. Here IVIG act similarly as in the immune thrombocytopenic purpura (ITP). They should be given to the mother weekly in large doses – on average 1 g/kg body weight, and to the child in case his/her platelet count falls below 50,000.

The varied mechanism of action presented above also allows paediatric haematologists to use IVIG in the treatment of an autoimmune haemolytic anaemia or a haemolytic disease of the newborn (HDN).

In patients with parvovirus B19-induced pure red cell aplasia (PRCA), immunoglobulins are used as a source of antibodies against parvovirus B19 and given as a single dose of 0.4 g IgG/kg every 28 days [41].

Immunoglobulins are also used to treat acquired haemophilia A. This is a severe diathesis induced by autoantibodies against factor VIII. The disease strikes mainly later in life; however, single cases have been reported in children as well. In about 50% of patients the disease is considered idiopathic; in the rest a concomitant disease is discovered at diagnosis, most often – a neoplasm (12.5 %), rheumatoid arthritis (14.6%), SLE (10.4%) or other autoimmune disorders (8.3%). A factor VIII inhibitor may also develop in pregnant and puerperal women (7–13.5 % of patients), especially in the first three months after birth. For the treatment of acquired haemophilia A IVIG is used in standard doses: 0.3–0.4 g/kg b.w./d for 5 days or 1–2 g/kg b.w./d for 2–5 days [42–45].
<table>
<thead>
<tr>
<th>Company</th>
<th>CSL Behring</th>
<th>Octapharma</th>
<th>Grifols</th>
<th>Kedrion</th>
<th>Baxter</th>
<th>Biotest</th>
<th>Octapharma</th>
<th>Biotest</th>
<th>Grifols</th>
<th>Baxter</th>
<th>CSL Behring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product</td>
<td>Sandoglobulin P</td>
<td>Octagam</td>
<td>Flebogamma Dif</td>
<td>Ig Vena</td>
<td>Gamma-gard S/D</td>
<td>Intratect</td>
<td>Intraglobulin F</td>
<td>Pentaglobin</td>
<td>Octagam</td>
<td>Intratect</td>
<td>Flebogamma Dif</td>
</tr>
<tr>
<td>Concentration</td>
<td>3–12%</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Form</td>
<td>lyophilizate</td>
<td>solution</td>
<td>solution</td>
<td>solution</td>
<td>lyophilizate</td>
<td>solution</td>
<td>solution</td>
<td>solution</td>
<td>solution</td>
<td>solution</td>
<td>solution</td>
</tr>
<tr>
<td>IgG%</td>
<td>≥ 96</td>
<td>≥ 95</td>
<td>≥ 97</td>
<td>≥ 95</td>
<td>≥ 90</td>
<td>≥ 96</td>
<td>≥ 95</td>
<td>≥ 95</td>
<td>≥ 96</td>
<td>≥ 97</td>
<td>≥ 98</td>
</tr>
<tr>
<td>IgG1%</td>
<td>57.70%</td>
<td>60%</td>
<td>66.60%</td>
<td>62.10%</td>
<td>&gt; 56, 9%</td>
<td>57%</td>
<td>62%</td>
<td>63%</td>
<td>60%</td>
<td>57%</td>
<td>67.80%</td>
</tr>
<tr>
<td>IgG2%</td>
<td>35.10%</td>
<td>32%</td>
<td>28.50%</td>
<td>34.80%</td>
<td>&gt; 16%</td>
<td>37%</td>
<td>34%</td>
<td>26%</td>
<td>32%</td>
<td>37%</td>
<td>&gt; 26.6%</td>
</tr>
<tr>
<td>IgG3%</td>
<td>3.10%</td>
<td>7%</td>
<td>2.70%</td>
<td>2.50%</td>
<td>&gt; 3.3%</td>
<td>3%</td>
<td>0.50%</td>
<td>4%</td>
<td>7%</td>
<td>3%</td>
<td>3.00%</td>
</tr>
<tr>
<td>IgG4%</td>
<td>4.10%</td>
<td>1%</td>
<td>2.20%</td>
<td>0.60%</td>
<td>&gt; 0.3%</td>
<td>3%</td>
<td>3.50%</td>
<td>7%</td>
<td>1%</td>
<td>3%</td>
<td>2.50%</td>
</tr>
<tr>
<td>IgA</td>
<td>≤ 40 mg/g</td>
<td>≤ 0.2 mg/mL</td>
<td>≤ 0.05 mg/mL</td>
<td>50 μg/mL</td>
<td>≤ 0.3 μg/mL</td>
<td>≤ 2 mg/mL</td>
<td>2.5 mg</td>
<td>6 mg</td>
<td>≤ 0.4 mg/mL</td>
<td>&lt; 1800 μg/mL</td>
<td>≤ 100 μg/mL</td>
</tr>
<tr>
<td>IgM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 mg/mL</td>
<td>≤ 0.3 mg/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specific indica-tions</td>
<td>myasthe-nia; CIDP; sepsis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CIDP</td>
<td></td>
<td></td>
<td></td>
<td>sepsis</td>
</tr>
<tr>
<td>Sodium content</td>
<td>present (NaCl)</td>
<td>none</td>
<td>&lt; 3.2 mmol/l</td>
<td>3 mmol/l</td>
<td>present (NaCl)</td>
<td>none</td>
<td>present (NaCl)</td>
<td>none</td>
<td>none</td>
<td>&lt; 3.2 mmol/l</td>
<td>none</td>
</tr>
<tr>
<td>Stabilizer</td>
<td>sucrose</td>
<td>maltose</td>
<td>d-sorbitol</td>
<td>maltose</td>
<td>human albumin</td>
<td>glycine</td>
<td>glucose</td>
<td>glucose</td>
<td>maltose</td>
<td>glycine</td>
<td>L-proline</td>
</tr>
<tr>
<td>Max. infusion rate</td>
<td>2.5 mL/min</td>
<td>5 mL/kg m.c./h</td>
<td>6 mL/kg m.c./h</td>
<td>1.85 mL/kg m.c./h</td>
<td>4 mL/kg m.c./h</td>
<td>1.9 mL/kg m.c./h</td>
<td>1.9 mL/kg m.c./h</td>
<td>1.7 mL/kg m.c./h</td>
<td>7.2 mL/kg m.c./h</td>
<td>1.9 mL/kg m.c./h</td>
<td>4.8 mL/kg m.c./h</td>
</tr>
<tr>
<td>Shelf life</td>
<td>3 years</td>
<td>2 years</td>
<td>2 years</td>
<td>For doses of: 1 g:2.5:10:0 g 2–8°C – 2 yrs for a dose of 5 g 2–8°C – 3 yrs</td>
<td>2 years</td>
<td>2 yrs in the fridge (2–8°C)</td>
<td>2 yrs in the fridge (2–8°C)</td>
<td>3 mths at room temp.</td>
<td>2 yrs at room temp.</td>
<td>2 years</td>
<td>2 yrs in the fridge (2–8°C)</td>
</tr>
<tr>
<td>Package size (in grams)</td>
<td>3 g 100 mL</td>
<td>6 g 250 mL</td>
<td>2.5 g 50 mL</td>
<td>5 g 100 mL</td>
<td>10 g 200 mL</td>
<td>1 g 20 mL</td>
<td>2.5 g 50 mL</td>
<td>5 g 100 mL</td>
<td>10 g 200 mL</td>
<td>0.5 g 10 mL</td>
<td>2.5 g 50 mL</td>
</tr>
</tbody>
</table>
Conclusion

Years of clinical practice allow us to conclude that intravenous immunoglobulin preparations are important in therapy of many diseases, including autoimmune blood disorders. High clinical efficacy on the one hand and relatively low incidence of adverse effects on the other make them particularly recommendable for patients in the youngest groups. It seems though that despite their qualities, IVIG are not sufficiently used in Poland. Statistics show that their use in our country is very low: only 12 g per 1000 inhabitants [46], while the average for Europe is 77 g per 1000 inhabitants and in the U.S. – as high as 144 g IgG per 1000 inhabitants! Additionally, according to National Health Found requirements, IVIGs should be used only in few indications described in each IVIG product characteristic (SPC). Worldwide use of IVIG is according to EBM (Evidence Based Medicine).

We hope that the short review of immunoglobulin preparations presented here will show doctors, especially paediatricians and pediatric haematologists, the benefits of using these drugs in the therapy of children with hematological diseases and will help them to choose a suitable preparation.

References


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