



REPORT OF A GROUP OF CONSULTANTS ON THE INDICATIONS
 AND CONTRAINDICATIONS FOR THE USE OF
 NORMAL AND SPECIFIC IMMUNOGLOBULINS

World Health Organization, Geneva, 18-20 June 1980



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1. INTRODUCTION

In the World Health Assembly resolution WHA28.72 concerning Blood and Blood Products, the Director-General was requested

- to take steps to develop good manufacturing practices specifically for blood and blood components in order to protect the health of both donor and recipients.

In the implementation of this request the International Requirements for the Collection, Processing and Quality Control of Human Blood were formulated and a number of problems were identified two of which concerned the indications and contraindications for the use of human coagulation factors and immune globulins. Accordingly, a Group of Consultants was convened to discuss the various issues concerned with these blood derivatives.

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The Group agreed that their prime concern was the assembly and presentation of the data on which governments may wish to base their decisions concerning the conditions for the use of these products, it being understood that the health authority of the government has the responsibility for the health of the nation.

2. IMMUNOGLOBULINS

Immunoglobulins are antibody concentrates prepared either from whole blood, from plasma obtained by plasmapheresis or from placental material; animal source material is also used. Although the majority of immunoglobulins are given by the intramuscular route intravenous preparations are used in special circumstances. For some products the efficacy has been demonstrated but for others there is no evidence that they are effective and this may be due to the quantity of antibodies used. If these preparations were available with a higher titre they may be effective but more information is needed before such a conclusion can be reached.

Immunoglobulins have a good record of safety provided they have been correctly prepared and administered. Nevertheless reactions have occurred, the majority of which have been local reactions. Systemic reactions are much less common. The substances in the immunoglobulins that may give rise to such reactions are not clearly defined. Immunoglobulin preparations are antibody concentrates from human or animal serum or plasma, which are produced and administered with the object of providing passive immunity in the recipient.

Normal immunoglobulin, human, is obtained from a plasma pool of a large number of normal donors and must have a minimum antibody titre against a number of different types of viral and bacterial antigens. Placental material¹ may be used also for the manufacture of normal immunoglobulin. The antibody titres in the immunoglobulins should be increased at least 10-fold over those in the source material.²

Specific immunoglobulins are produced from source materials with increased antibody titres which have been selected by screening, or obtained by immunizing or hyper-immunizing donors. As compared to normal immunoglobulins, specific immunoglobulins must have a significantly increased antibody titre against at least one antigen.

Specific animal immunoglobulins are mostly obtained from hyper-immunized horses, but may be obtained from other animal species.

The protein concentration in normal immunoglobulins, human, lies between 15% and 18%, whereas that of specific human immunoglobulins is between 10% and 18%. Such preparations are intended for intramuscular administration whereas human immunoglobulins for intravenous use are administered as approximately 5% protein solutions. Animal immunoglobulins are available in solutions containing 10% to 20% protein. Higher purity preparations of both human and animal origin can be obtained by treatment with proteolytic enzymes; pepsin is usually used.

Immunoglobulin preparations given by the intramuscular route usually contain 1:10 000 thiomersal as a preservative, and 0.3 M glycine as a stabilizer. In the liquid form, they can be stored for up to three years at 5°C ± 3°C.

The immunoglobulin G molecule of human immunoglobulins may be split during storage and such degradation is attributable to activated plasma proenzymes which may be present as contaminants.

¹ WHO Technical Report Series, 1978, No. 626, Part B, section 3.7.

² WHO Technical Report Series, 1967, No. 361, Part A, section 3.4.7.1, p. 52.

3. HUMAN IMMUNOGLOBULINS FOR INTRAVENOUS USE

If a human immunoglobulin prepared for intramuscular use is administered by the intravenous route particularly in patients with agammaglobulinaemia severe, life-threatening anaphylactoid reactions may occur. Therefore, a human immunoglobulin must not be administered to these patients unless especially prepared for intravenous use. Neither the pathogenesis of these severe adverse reactions, nor the substances in the immunoglobulins causing them are fully understood. The presence of immunoglobulin aggregates may play an important role.

Immunoglobulins for intravenous use can be classified into:

- (i) enzymatically modified immunoglobulin G preparations;
- (ii) chemically modified immunoglobulin G preparations; and
- (iii) further purified immunoglobulin G preparations.

(i) Enzymatically modified

For the manufacture of the first group of products various proteolytic enzymes, in particular pepsin and plasmin are used. The resulting fragmented immunoglobulin G preparations contain up to 50% intact immunoglobulin G. In the majority of preparations, however, most of the immunoglobulin G molecules are fragmented. While the rate of adverse reactions is very low with the highly fragmented preparations, a greater incidence of adverse reactions is observed with the less fragmented preparations. The biological half-life of these products depends on the extent of enzymatic degradation.

The half-life of the extensively split preparations is a few hours whereas that of the less fragmented ones may be as long as several days.

(ii) Chemically modified

The chemically modified immunoglobulins are treated with low molecular weight chemical agents known to be reactive with proteins either as intact globulins or after reductive splitting of the immunoglobulin G molecule. As compared with the enzymatically-modified immunoglobulin G, the chemically modified preparations have an improved biological half-life which, however, is not as long as that of the native immunoglobulin G. Some of the immunoglobulins in this group have been observed to cause adverse reactions in some patients.

(iii) Purified immunoglobulins

The third group of immunoglobulin G preparations for intravenous use contain a high quantity of purified immunoglobulin G. The manufacturing process is designed to avoid the generation of, destroy, or remove any substance likely to be responsible for known adverse reactions. These preparations have a normal biological half-life for globulins of between 23 and 28 days. Their immunoglobulin G molecules are largely intact, and their Fc-piece retains their full biological activity.

It is well known that the Fc-piece in the immunoglobulin G molecule is responsible for a series of important biological activities, including phagocytosis of antibody-coated microorganisms as well as their intracellular killing, and binding of antigen-antibody complexes to Fc-receptors of cells such as macrophages. This Fc-piece property is significantly impaired in chemically modified immunoglobulin G preparations, and is altogether absent in the enzymatically modified ones.

The safety of immunoglobulin G preparations for intravenous use in recipients known to be reactive needs further investigation. In particular, patients with agammaglobulinaemia are known to be hyperreactive to immunoglobulin preparations. Such patients may tolerate a series of a particular intravenous preparation on many occasions but may develop severe side reactions when the same preparation is administered on one particular occasion.

4. SOURCE MATERIAL

A. Human blood

Plasma containing adequate quantities of antibodies for the preparations of immunoglobulins can be obtained from whole blood and by plasmapheresis. The methods of donor selection and donor protection must satisfy the Requirements for the Collection, Processing and Quality Control of Human Blood and Blood Products.¹

Immunoglobulins can be obtained either from the plasma of donors who have acquired immunity through natural exposure to an antigen or from the plasma of donors who have been on active immunization programmes. The identification of donors with elevated titres to a specific antibody, can be accomplished by screening random donors or by the selection of individuals known to be convalescing from specific diseases.

When there is a medically valid need for specific immunoglobulins which are not available in sufficient quantities from the donor groups mentioned above, hyperimmunization may be undertaken. Hyperimmunization may be defined as the use of vaccines or immunogens, including erythrocytes for either antibody stimulation *de novo* or for increasing the titre of existing antibodies in donors utilizing doses and schedules which differ from those recommended for routine immunization. All antigens used for the immunization of donors must be registered or recognized by or their use notified to the National Health Authority and must be provided by a registered establishment.

The selection of the antigen, route of injection, dose, schedule, observation for adverse reactions and antibody response shall be made by a licensed physician.

The schedule of hyperimmunization for each antigen should be submitted to the National Health Authority and every effort should be made to use the minimum dose and number of antigen injections. When designing any immunization programme the following should be taken into consideration at least:

- (a) the method of antibody assay;
- (b) the minimum level of antibody required;
- (c) data supporting the dose intervals between injections and total dosage proposed for each antigen;
- (d) the total amount of a specific antigen which can be administered to a prospective donor for the responsible physician to decide whether the donor is a responder or non-responder.

No donor shall be hyperimmunized with more than one immunizing preparation.

The donor should be:

- (i) informed of the procedures by a licensed physician and encouraged to take part in a free discussion, which in some countries, is achieved initially in small groups of potential donors;
- (ii) encouraged to seek advice from the family doctor before agreeing to immunization;
- (iii) informed that any licensed physician of their choice will receive all information on the proposed immunization procedure; and
- (iv) required to indicate his agreement by signing an informed-consent form.

¹ WHO Technical Report Series, 1978, No. 626, Part A, section 5, pp. 38-44.

B. Human placenta

Whole placenta, placental blood or serum, and retroplacental blood or serum may all serve as source material for normal immunoglobulin. All placental material should be obtained from healthy persons and should be collected under conditions that reduce the risk of bacterial contamination to a minimum.

It must be emphasized that the placental material should be hepatitis B surface antigen negative when tested by sensitive techniques such as third generation tests. Hepatitis B surface antigen positive placental material must not be used for the preparation of human immunoglobulins.

C. Animal blood

The source material used for the preparation of immunoglobulins from immunized animals is serum or plasma prepared from whole blood collected by venepuncture, in such a manner that sterility is maintained. The animal source material used for such purposes must satisfy the WHO Requirements for Immune Sera of Animal Origin.¹ A special room shall be set aside for the collection of the source material and the processing shall be done also in a separate area.

Only healthy animals shall be used; cattle shall be shown to be free from tuberculosis and horses shall be free from glanders. The animals shall not have received penicillin or streptomycin.

The areas in which the immunoglobulins are prepared shall satisfy the revised General Requirements for Manufacturing Establishment and Control Laboratories.²

It is recommended that plasma or serum from all sources should be stored and transported in the frozen state (-20°C or below) in order to minimize bacterial growth and to maintain antibody levels. Exceptions to this principle may be made only by the National Health Authority.

5. QUALITY CONTROL OF IMMUNOGLOBULINS

The immunoglobulins shall satisfy the Requirements for the Collection and Quality Control of Human Blood and Blood Products.³ In addition the following shall apply:

(i) Normal immunoglobulin shall be prepared from pooled source material by a method that has been shown to be capable of concentrating at least two different antibodies, one viral and one bacterial for which an international standard or reference preparation is available. In addition it is recommended that hepatitis B surface antibody be present.⁴

(ii) Periodic tests shall be made to determine the proportion of aggregated and fragmented immunoglobulin present during the dating period of all immunoglobulins. It is desirable that no aggregates ($S > 12.0$) are present and that at the end of the dating period at least 80% of the protein must be intact as assessed by ultra-centrifugation, electrophoresis or gel filtration chromatography.

¹ WHO Technical Report Series, 1969, No. 413, Part A, section 3, pp. 52-55.

² WHO Technical Report Series, 1966, No. 323.

³ WHO Technical Report Series, No. 626, 1978, Annex 1, Part D, section 4, pp. 71-76.

⁴ When immunoglobulins have transmitted hepatitis B they have been associated with the presence of hepatitis B surface antigen HBsAg and no detectable hepatitis B surface antibody.

- (iii) The immunoglobulin shall be composed of not less than 90% of immunoglobulin G as determined by an approved method (radial immunodiffusion is not considered a valid assay when fragmented immunoglobulin is present).
- (iv) The storage of liquid immunoglobulin shall be at $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ and the storage of freeze-dried preparations shall be below 25°C .

The expiry date of the liquid preparations shall be not more than three years from the date of the first satisfactory potency test provided that 80% or more of the immunoglobulin is intact.

6. THE USES OF IMMUNOGLOBULINS

The uses of immunoglobulins are the following:

(a) Normal immunoglobulins, human

Normal immunoglobulin is effective in humoral immunodeficiencies and particularly for the prophylaxis of measles and hepatitis A. Current normal immunoglobulin preparations may be effective also for the prophylaxis of hepatitis B. Several studies demonstrate that normal immunoglobulin is not effective for prophylaxis against rubella or mumps at the doses administered.

(b) Human specific immunoglobulins

- (i) Tetanus immunoglobulin is used for the prophylaxis of wounded patients who have not had an adequate active immunization against tetanus. Tetanus immunoglobulin is recommended also for the treatment of tetanus.
- (ii) Hepatitis B immunoglobulin is used for prophylaxis immediately after exposure and, in such cases, high titre hepatitis B immunoglobulin may be no more effective than normal immunoglobulin.
- (iii) Rabies immunoglobulin is used for post-exposure prophylaxis in conjunction with active immunization.
- (iv) A limited supply of vaccinia immunoglobulin should be available in case of emergencies.
- (v) Varicella Zoster immunoglobulin is used for the prophylaxis of immune-suppressed patients who have had contact with chickenpox.
- (vi) $\text{Rh}_0(\text{D})$ immunoglobulin is used for the suppression of the development of anti-D antibodies, particularly in potentially fertile $\text{Rh}_0(\text{D})$ negative females, in order to prevent an Rh haemolytic disease of the newborn in the event of the mother being transfused with $\text{Rh}_0(\text{D})$ positive red blood cells.
- (vii) Poliomyelitis immunoglobulin may be of use in the prophylaxis of unvaccinated subjects exposed to special risks.

7. ADVERSE REACTIONS TO IMMUNOGLOBULINS

Immunoglobulins when administered intramuscularly are considered not to cause immediate side reactions in the majority of patients, but some adverse reactions may occur. These are:

- (i) The most common adverse reaction is local pain at the injection site. Less common side effects include flushing, headache, chills, and nausea. Severe reactions involve an anaphylactoid type response.

- (ii) Patients with isolated immunoglobulin A (IgA) deficiency may develop antibodies to IgA and therefore could have an anaphylactic reaction to subsequent administration of blood products.
- (iii) In general immunoglobulins have a record of freedom from hepatitis transmission but a few lots have been found to be infective for hepatitis B.
- (iv) Most of the immunoglobulin preparations may induce adverse reactions, including anaphylactoid responses when administered intravenously and these seem to be related to the rate of infusion.
- (v) The underlying mechanism for the occurrence of adverse side reactions is unknown. Several hypotheses have been considered including the presence of high molecular weight components of immunoglobulins which may activate complement. Contaminants such as pre-kallikrein activator, kallikrein, factor XIa, have been suggested also as possible agents.
- (vi) The administration of equine or other animal products is associated with considerable risk of adverse side reactions which include: acute febrile reactions, serum sickness, and anaphylactic reactions. It is recommended, therefore, to use human immunoglobulins whenever possible.

8. THE NEED FOR FURTHER STUDIES

The Group agreed that further information was needed on the following points:

1. Although there are clear indications for the efficacy of some specific immunoglobulins others have been ineffective and it is important to determine whether preparations of higher antibody content would be effective.
2. The different methods of preparation of the immunoglobulins from plasma particularly with respect to the digestion procedure can have a marked effect upon the physical state of the immunoglobulins. In addition some procedures may remove a fraction of the globulins. A study of the method of preparation yielding the most effective immunoglobulins is important.
3. Although immunoglobulins have a good record of safety there are contaminants in the final products and it is important to determine whether any such contaminants are responsible for, or contribute to the rare reactions that do occur.
4. There is a need to investigate the adverse reactions to intravenous immunoglobulins especially in patients with agammaglobulinaemia who are hyperreactive to immunoglobulin preparations.
5. The efficacy of the different intravenous preparations in the prevention and treatment of various infectious diseases, particularly in immune compromised patients needs further study.
6. It would be useful to have more information on the immunization schedule for the hyper-immunization of donors of hyperimmune plasma.

ANNEX

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