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The present invention relates to the use of proline for reducing the viscosity of a protein preparation.

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(54) Title: IMMUNOGLOBULIN PREPARATION

(57) Abstract: The present invention relates to the use of proline for reducing the viscosity of a protein preparation.

Immunoglobulin preparation

The present invention relates to the use of proline, and in particular L-proline, to reduce the viscosity of a protein preparation, preferably of an immunoglobulin (Ig) preparation, more preferably of an Ig preparation comprising Ig in a mass-volume percentage of at least 18%.

The present invention further relates to a process for preparing an Ig preparation comprising Ig in a mass-volume percentage of at least 18%, to an Ig preparation obtainable by said process and to the use of said Ig preparation for preparing a medicament for the subcutaneous administration to a human.

Primary immunodeficiency (PID) disorders, such as common variable immunodeficiency (CVID) and X-linked agammaglobulinemia, predispose patients to recurrent infections. These patients require immunoglobulin (Ig) replacement therapy, which can be administered intravenously (IVIg) or subcutaneously (SCIg). Immunoglobulin therapy with IVIg or SCIg has also been shown to be useful in the treatment of other conditions, for example in the treatment of inflammatory and autoimmune conditions, as well as certain neurological disorders.

If immunoglobulin is administered via the more common intravenous route, a sharp rise in serum immunoglobulin level is produced which declines as Ig redistributes into the extravascular space over the next 48 hours, and then falls with first-order kinetics over approximately three weeks before intravenous administration is repeated. Many patients report feeling a “wear-off”-effect during the last week of the dosing interval, in particular malaise, fatigue, arthralgias, myalgias or increased susceptibility to infections.

Considering the drawbacks of intravenous Ig administration, Ig administration via

the subcutaneous route has become increasingly popular in recent years. The method does not require venous access, is associated with only few systemic side effects and has been reported to improve patient's quality of life.

One of the major challenges in the formulation of an Ig preparation, and in particular of an Ig preparation for subcutaneous administration, lies in the fact that Ig dissolved in aqueous solution tend to aggregate and form precipitates if not sufficiently stabilised with appropriate additives. Carbohydrates are sometimes used as stabilisers; however, increasing concentrations of carbohydrates are associated with poor tolerability, in particular in the treatment of patients with impaired kidney function (e.g. diabetes patients).

With regard to the stabilisation of monomeric Ig, particularly good results have been achieved by using a basic or non-polar amino acid as a stabiliser. As for example disclosed in WO 2005/049078, the addition of basic or non-polar amino acids and the adjustment of the pH of the final preparation have been found to markedly decrease the formation of aggregates and thus increase the stability of those preparations, particularly at ambient temperature.

When using the subcutaneous route for Ig-treatment of certain indications, relatively large volumes of Ig preparations need to be administered. With the currently available Ig formulations of up to 16% (160 g/l), the inability of tissues to accept large volumes of infused Ig preparation rapidly presents a limitation to subcutaneous administration. Thus, patients receiving Ig via the subcutaneous route need a relatively frequent administration of relatively small volumes at multiple sites. Some patients and physicians regard the multiple sites and frequent subcutaneous infusions as burdensome enough to decline or recommend against SCIg therapy.

In view of this, Ig preparations having a higher Ig concentration would thus be desirable. However, an increase in the Ig concentration goes along with a non-linear increase in viscosity which rapidly presents a limitation to the subcutaneous administration with conventional means. Specifically, highly viscous Ig preparations

develop a high back-pressure and therefore compromise proper infusion by the infusion pump. In particular, a prolonged duration of administration compared to preparations having a lower concentration can be expected. This might consequently lead to a decrease in the acceptance of the subcutaneous route.

Also with regard to the manufacturing process, the handling of a highly viscous Ig preparation is relatively cumbersome.

It is thus an object of the present invention to provide a simple means for reducing the viscosity of a protein preparation, particularly of an Ig preparation and more particularly of an Ig preparation having a high Ig concentration.

It is a further object of the present invention to provide a highly concentrated Ig preparation, which is suitable for subcutaneous administration and which by at least maintaining the efficacy of currently available Ig preparations allows for an administration of smaller volumes in a fast and simple manner.

The problem is solved by the subject matter according to the independent claims. Preferred embodiments are defined in the dependent claims.

According to a first aspect, the present invention thus relates to the use of proline for reducing the viscosity of a protein preparation, preferably of an Ig preparation.

The term “viscosity” as used in the context of the present invention means dynamic viscosity. The SI physical unit of dynamic viscosity is millipascal second (mPa·s).

The viscosity can for example be determined by a falling ball viscosimeter (“Kugelfallviskosimeter”) according to Höppler in accordance with the European Pharmacopoeia Version 6.0 at 2.2.49 and the requirements of DIN 53015. Thereby, the rolling time of a ball or sphere in a tube or capillary of defined dimensions and having a defined slope is determined. Based on the rolling time, the viscosity of the liquid in the tube or capillary can be determined. The values given in the present application text have been determined by the above principle using a microviscosimeter of the type AMV200 (of Anton Paar GmbH, Graz, Austria). The

measurements have been made at a temperature of 20.0°C +/- 0.1°C.

It has surprisingly been found by the present inventors that by adding proline, and in particular L-proline, a relatively low viscosity of the Ig preparation can be achieved even if the concentration of Ig is high. The same effect can be achieved for other protein preparations, for example for an albumin preparation.

Proline has been reported to have a stabilising effect on protein preparations, its effect of reducing the viscosity of a protein preparation, and in particular of an Ig preparation, has however nowhere been considered so far.

The presence of proline thus has the double beneficial effect of stabilising Ig on the one hand, and thus allowing to obtain a preparation having a very high stability over a relatively long period of time, and of providing a low viscosity on the other hand, thus allowing administration of the preparation in a fast and simple manner.

As mentioned, the effect of reducing the viscosity is of particular relevance for Ig preparations having a high Ig concentration, specifically Ig preparations having a mass-volume percentage of at least 15%.

In a preferred embodiment, the Ig comprised in the Ig preparation to which the present invention relates essentially consists of IgG. In other preferred embodiments of the invention, the Ig comprised in the Ig preparation essentially consists of IgA or essentially consists of IgM.

In the sense of the present invention, a mass-volume percentage of 15% means 150 g per liter.

According to a second aspect, the present invention also relates to a process for preparing an immunoglobulin preparation comprising immunoglobulin in a mass-volume percentage of at least 18%, wherein said process comprises the step of adding proline to reduce the viscosity of the preparation.

Thus, an Ig preparation having a high Ig concentration and having at the same time

a relatively low viscosity can be obtained in a very simple and straightforward manner.

According to a particularly preferred embodiment of the process of the present invention, proline is added at a mass-volume percentage of the immunoglobulin of less than 15%, preferably less than 14%, more preferably less than 13%, and most preferably less than 12%, before concentrating the preparation to the mass-volume percentage of the immunoglobulin of at least 18%.

In contrast to the conventional process for the formulation of Ig preparations, the stabiliser – in this case proline - is added before the final concentration step. Thus, the protein in the concentrated product is less subject to stress conditions (e.g. shear forces) as it would be the case if the stabiliser is added after the concentrating step. The process according to this embodiment thus allows for a very gentle treatment of the product.

As set forth above, proline used in the process of the present invention is preferably L-proline.

According to a further preferred embodiment of the process of the present invention, the amount of proline added is such that the concentration of proline in the immunoglobulin preparation ranges from about 10 to about 1000 mmol/l, more preferably from about 100 to about 500 mmol/l, and most preferably is about 250 mmol/l.

According to a particularly preferred embodiment of the process, an Ig preparation comprising Ig in a mass-volume percentage ranging from 18% to less than 20% is prepared, whereby proline is added in an amount such that the viscosity is less than 13 mPa·s, preferably less than 11 mPa·s, more preferably less than 10 mPa·s, and most preferably less than 9 mPa·s.

According to an alternative particularly preferred embodiment, an Ig preparation comprising Ig in a mass-volume percentage of at least 20% is prepared, wherein

proline is added in an amount such that the viscosity is less than 19 mPa·s, preferably less than 17 mPa·s, more preferably less than 15 mPa·s, and most preferably less than 13 mPa·s.

Having learned from the teaching of the present invention, a skilled person readily realizes how to choose the respective amounts of proline in order to achieve the viscosity aimed for.

According to a third aspect, the present invention relates to an Ig preparation obtainable by the above process.

In particular, the present invention thus relates to an Ig preparation comprising Ig in a mass-volume percentage ranging from 18% to 20%, wherein said preparation comprises proline in an amount such that the viscosity is less than 13 mPa·s, preferably less than 11 mPa·s, more preferably less than 10 mPa·s, and most preferably less than 9 mPa·s.

More particularly, the present invention relates to an Ig preparation comprising Ig in a mass-volume percentage of 18% to 19%, wherein said preparation comprises proline in an amount such that the viscosity is less than 12 mPa·s, preferably less than 11 mPa·s, and to an Ig preparation comprising Ig in a mass-volume percentage of more than 19% to less than 20%, wherein said preparation comprises proline in an amount such that the viscosity is less than 15 mPa·s, preferably less than 13 mPa·s.

Alternatively, the present invention also relates to an Ig preparation comprising Ig in a mass-volume percentage of at least 20%, wherein said preparation comprises proline in an amount such that the viscosity is less than 19 mPa·s, preferably less than 17 mPa·s, more preferably less than 15 mPa·s, and most preferably less than 13 mPa·s.

More particularly, the present invention relates to an Ig preparation comprising Ig in a mass-volume percentage of more than 20% and at the most 22%, wherein said

preparation comprises proline in an amount such that the viscosity is less than 19 mPa·s, preferably less than 17 mPa·s, more preferably less than 14 mPa·s, most preferably less than 12 mPa·s, and to an Ig preparation comprising Ig in a mass-volume percentage of more than 22%, wherein said preparation comprises proline in an amount such that the viscosity is less than 27 mPa·s, more preferably less than 20 mPa·s.

Apart from the Ig preparations defined above, the following Ig preparations can be achieved by using proline according to the present invention:

an Ig preparation comprising Ig in a mass-volume percentage of more than 16% and at the most 17%, wherein said preparation comprises proline in an amount such that the viscosity is less than 8 mPa·s, preferably less than 7 mPa·s, more preferably less than 6 mPa·s; and

an Ig preparation comprising Ig in a mass-volume percentage of more than 17% and less than 18%, wherein said preparation comprises proline in an amount such that the viscosity is less than 10 mPa·s, preferably less than 9 mPa·s, more preferably less than 8 mPa·s.

For the purpose described above, highly concentrated Ig preparations, in particular Ig preparations comprising Ig in a mass-volume percentage of about 20%, are particularly preferred.

Such highly concentrated Ig preparations are preferably used for the subcutaneous administration to patients, by way of a non-limiting example for the treatment of PID or CVID. Preferably, the Ig comprised in the Ig preparation of the present invention essentially consists of IgG, as mentioned above, but is in no way limited thereto. In other preferred embodiments of the preparation of the present invention, the Ig comprised essentially consists of IgA or essentially consists of IgM .

Given the high concentration of Ig, the present invention allows smaller volumes of the preparation to be administered to the patient, while maintaining the efficacy

compared to conventionally available preparations having a lower Ig concentration.

Despite of its relatively high Ig concentration, the present invention allows the preparation to be administered in a fast and simple manner due to its low viscosity. In particular, conventional means currently used for the conventional Ig preparations of lower concentration can be used for the subcutaneous administration.

Given its low viscosity, the Ig preparation of the present invention allows, for example, administration by direct manual push from a syringe. The possibility to use simple devices, such as a conventional syringe, increases the acceptance of the subcutaneous administration and ultimately lowers the cost of the treatment regimen.

Apart from its very low viscosity, the Ig preparation of the present invention has very high storage stability of at least 24 months when stored at room temperature. The room temperature stability provides improved flexibility and convenience of administration for patients with e.g. PID or CVID, compared with other preparations that must be kept refrigerated.

As set forth above, proline is preferably L-proline. L-proline is normally present in the human body and has a very favourable toxicity profile. The safety of L-proline was investigated in repeated-dose toxicity studies, reproduction toxicity studies, mutagenicity studies and safety pharmacology studies, and no adverse effects were noted.

As also set forth above, the Ig preparation preferably comprises proline, and in particular L-proline in a concentration ranging from about 10 to about 1000 mmol, preferably from about 10 to about 500 mmol/l, more preferably from about 100 to about 500 mmol/l, and most preferably is about 250 mmol/l. L-proline used in this concentration range is rapidly cleared after administration of the preparation without any accumulation.

As sufficient stabilisation is achieved by the presence of proline, and in particular L-proline, the addition of carbohydrates as stabilisers can be avoided. According to a preferred embodiment of the present invention, the preparation is thus essentially free of carbohydrates, which may have a beneficial effect on tolerability.

According to a further preferred embodiment, the Ig preparation has a pH of 4.2 to 5.4, preferably 4.6 to 5.0, most preferably about 4.8, which further contributes to the high stability of the preparation.

As already stated above, an aspect of the invention is the use of a single agent for reducing the viscosity and increasing the stability of an immunoglobulin preparation, wherein the single agent is proline, preferably L-proline. Preferably, the amount of proline added is such that the concentration of proline in the immunoglobulin preparation ranges from 10 to 1000 mmol/l, more preferably from 10 to 500 mmol/l, even more preferably from 100 to 500 mmol/l, most preferably about 250 mmol/l.

Preferably, the immunoglobulin preparation comprises immunoglobulin in a mass-volume percentage of at least 18%, more preferably at least 19%, most preferably at least 20%. Preferably, the immunoglobulin of the immunoglobulin preparation is essentially pure IgG. Alternatively, the immunoglobulin of the immunoglobulin preparation is essentially pure IgA or essentially pure IgM.

As given above, the advantages of the present invention are particularly apparent if the Ig preparation is used for subcutaneous administration to a human. The present invention thus also relates to the use of the Ig preparation for the preparation of a medicament for subcutaneous administration to a human. As for example reported by S. Misbah et al, Clinical and Experimental Immunology, 158 (Suppl. 1); pp. 51 – 59, there are various advantages of the subcutaneous administration of the preparation over the intravenous administration. In particular, venous access is not required and the need for premedication with corticosteroids and anti-histamines is reduced.

Also, when using the subcutaneous route the marked peaks typically seen with

monthly IVIg infusions are damped and persistently elevated Ig levels are obtained leading to a reduction in systemic side effects.

Due to the low viscosity of the Ig preparation of the present invention, administration can be performed in a very fast and simple manner, in particular by direct manual push from a syringe, as mentioned above. Thus, the present invention allows self-administration of the Ig preparation by many patients at home, ultimately resulting in better convenience, better quality of life and fewer absences from work.

In particular, the present invention allows the preparation to be administered by the so-called “rapid push” technique described in the above-mentioned review article of S. Misbah et al. in the context of an Ig preparation of lower concentration (Vivaglobin® comprising Ig in a mass-volume percentage of 16%). According to said technique, a syringe and a 23-25-gauge butterfly needle is used to push SCIg under the skin as fast as the patient is comfortable with (usually 1 to 2 cc/min). Administration by said technique thus usually takes only between 5 and 20 minutes.

A specific, non-limiting example of a process for preparing an IgG preparation of the present invention is given in the following:

Example

Process for preparing IgG preparation

1. Plasma pool

Igs were isolated from pooled human plasma derived from numerous (> 1000) donors.

Starting from this suspension, the following steps were taken:

a) precipitating the human plasma using ethanol to obtain a precipitate and a

supernatant;

b) subjecting the re-suspended precipitate obtained under a) to octanoic acid fractionation followed by filtration and diafiltration;

c) incubating the filtrate obtained under b) at a pH of about 4, followed by filtration;

d) subjecting the filtrate obtained under c) to anion exchange chromatography to obtain an eluate comprising Ig, said Ig comprising IgG in a purity of more than 96%;

e) subjecting the eluate obtained under d) to nanofiltration to obtain a filtrate which is essentially virus free;

f) subjecting the filtrate obtained under e) to diafiltration and ultrafiltration to obtain a filtrate having a mass-volume percentage of IgG of about 12%;

g) adding proline, and in particular L-proline, to the filtrate obtained under f);

h) concentrating the filtrate comprising proline to obtain an IgG preparation having a mass-volume concentration of IgG of about 20%; and

i) adding polysorbate 80 to the IgG preparation.

The constituents and their respective amount in the final preparation are given in Table 1. Also given are the values of selected physicochemical parameters as well as the purity of the final Ig preparation.

Table 1:

Composition	
Constituent	**Target Value**
Protein	200 g/L
L-Proline*	250 mmol/L (28.8 g/L)
Polysorbate 80*	Traces
Sodium	≤10 mmol/L
Physicochemical properties	
Parameter	**Target Value**
Osmolality	~380 mOsmol/kg bw
pH**	4.8 (measured at 1% protein concentration in NaCl 0.9%)
Viscosity	14.71 mPa·s[#]
Purity	
Protein	**Typical value**
IgG	> 98%
IgA	< 50 mg/L
Monomers + dimers	≥ 90.0%

*L-proline and polysorbate 80 used are of non-animal origin in order to minimise the risk of contaminating the product with transmissible spongiform encephalopathy pathogens.

**To attain the optimum measurement, pH is determined in a water-diluted solution (1% protein [10 g/L] as standard).

#Mean value from 28 lots. Viscosity measured at room temperature

Further, the viscosity of numerous IgG preparations according to the present invention (comprising L-proline in a concentration of 250 mmol +/- 40 mmol/l) has been determined, said preparations differing in the specific mass-volume percentage of IgG. Some measurements with lower proline concentrations (10 to 100mmol/l) have also been included. The viscosity has been determined by a falling sphere viscosimeter ("Kugelfallviskosimeter") according to Höppler in accordance with the European Pharmacopoeia Version 6.0 at 2.2.49 and the requirements of DIN 53015. In particular, a microviscosimeter of the type AMV200 (of Anton Paar GmbH, Graz, Austria) has been used. The measurements have been made at a temperature of 20.0°C +/- 0.1°C.

The respective results are listed in Table 2:

Table 2:

Mass concentration of IgG (g/l)	Viscosity of preparation (mPa·s)	Proline concentration (mmol/l)
97.7	3.09	250
147.5	6.69	250
173.9	7.21	250
177.5	8.79	250
178.4	7.78	250
193.7	11.15	250
198.6	11.25	250
199.9	11.25	250
215.8	16.65	250
219.8	16.75	250
222.1	16.85	250
150	5.7	100
143	5.8	50
144	6.0	10

In comparison, the viscosity of numerous Ig preparations devoid of proline has been determined, the results of which being listed in Table 3:

Table 3:

Mass concentration of IgG (g/l)	Viscosity of preparation (mPa·s) (without proline)
108.6	2.69
146.3	3.82
154.9	7.38
185.9	13.9
194.8	16.95
207.6	21.9
227.8	34.45

According to Tables 2 and 3, the presence of proline leads to a reduction in viscosity at protein concentrations higher than 15%. At a mass concentration of about 200 g/l (mass-volume percentage of about 20%), the viscosity of the preparation according to the present invention is lower than 12 mPa·s and thus far lower than the viscosity of the preparation devoid of proline.

Claims

1. Use of proline for reducing the viscosity of an immunoglobulin preparation, comprising immunoglobulin in a mass-volume percentage of at least 15%, and wherein proline is used at a concentration of 100 to 500 mmol/l and wherein the viscosity is measured with a falling ball viscosimeter at 20°C.

2. Use according to claim 1, wherein the immunoglobulin preparation comprises immunoglobulin in a mass-volume percentage of at least 18%.

3. Use according to claim 1 or claim 2, wherein proline is L-proline.

4. Process for preparing an immunoglobulin preparation comprising immunoglobulin in a mass-volume percentage of at least 18%, wherein proline is added at a mass-volume percentage of the immunoglobulin of less than 15% before concentrating the immunoglobulin preparation to the mass-volume percentage of the immunoglobulin of at least 18% and wherein the viscosity is measured with a falling ball viscosimeter at 20°C.

5. Process according to claim 4, wherein proline is L-proline.

6. Process according to claim 4 or claim 5, wherein the immunoglobulin of the immunoglobulin preparation essentially consists of IgG.

7. Process according to any one of claims 4 to 6, wherein the amount of proline added is such that the concentration of proline in the immunoglobulin preparation ranges from 100 to 500 mmol/l.

8. Process according to any one of claims 4 to 7 for preparing an immunoglobulin preparation comprising immunoglobulin in a mass-volume percentage ranging from 18% to less than 20%, wherein proline is added in an amount such that the viscosity is less than 13 mPa·s, whereby the viscosity is measured with a falling ball viscosimeter at 20°C.

9. Process according to any one of claims 4 to 7 for preparing an immunoglobulin preparation comprising immunoglobulin in a mass-volume

percentage of at least 20%, wherein proline is added in an amount such that the viscosity is less than 19 mPa·s.

10. Immunoglobulin preparation obtained by the process of any one of claims 4 to 9.

11. Immunoglobulin preparation according to claim 10 comprising immunoglobulin in a mass-volume percentage ranging from 18% to less than 20%, wherein said preparation comprises proline in an amount such that the viscosity is less than 13 mPa·s, whereby the viscosity is measured with a falling ball viscosimeter at 20°C.

12. Immunoglobulin preparation obtained by the process of any one of claims 4 to 9, comprising immunoglobulin in a mass-volume percentage of at least 20%, wherein said preparation comprises proline in an amount such that the viscosity is less than 19 mPa·s, or comprising immunoglobulin in a mass-volume percentage ranging from 18% to less than 20%, wherein proline is added in an amount such that the viscosity is less than 13 mPa·s, whereby the viscosity is measured with a falling ball viscosimeter at 20°C.

13. Immunoglobulin preparation according to claim 12, comprising immunoglobulin in a mass-volume percentage of about 20%.

14. Immunoglobulin preparation according to any one of claims 10 to 13, wherein the preparation has a pH ranging from 4.2 to 5.4.

15. Immunoglobulin preparation according to any one of claims 10 to 14, wherein the preparation is essentially free of carbohydrates.

16. Immunoglobulin preparation according to any one of claims 10 to 15 for the subcutaneous administration to a human.

17. Immunoglobulin preparation according to claim 16 for the subcutaneous administration to a human by direct manual push from a syringe.

18. Use of a single agent for reducing the viscosity and increasing the stability of an immunoglobulin preparation comprising immunoglobulin in a mass-volume percentage of at least 15%, wherein the single agent is proline at a concentration of 100 to 500 mmol/l and wherein the viscosity is measured with a falling ball viscosimeter at 20°C.