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What's happening?

The Norwegian plasma fractionation project—a 12 year clinical and economic success story

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Abstract

The establishment of the Norwegian Fractionation Project (Project) was of major importance in preserving national self-sufficiency when plasma, cryoprecipitate and small batch factor IX-concentrates were replaced by virus inactivated products in the last part of the 1980s. Fractionation was performed abroad by contract with Octapharma after tenders on the European market. All Norwegian blood banks (>50) participated in the Project. Total yearly production was 50–60 tons of mainly recovered plasma. From 1993 solvent detergent (SD) treated plasma has replaced other plasma for transfusion.

The blood banks paid for the fractionation and/or viral inactivation process, while the plasma remained the property of the blood banks and the final products were returned to the blood banks. The Project sold surplus products to other Norwegian blood banks and the majority of the coagulation factor concentrates to The Institute of Haemophilia and Rikshospitalet University Hospital. Both plasma and blood bank quality was improved by the Project. Clinical experience with the products has been satisfactory and self-sufficiency has been achieved for all major plasma proteins and SD plasma, but a surplus exceeding 3 years consumption of albumin has accumulated due to decreasing clinical use.

The Project has secured high yields of the fractionated products and the net income from the produced products is NOK 1115 (140 € or US$) per litre plasma. An increasing surplus of albumin and the possibility of significant sales abroad of currently not fractionated IVIgG, could lead to a reorganisation of the Project from that of a co-ordinator to a national plasma handling unit. This unit could buy the plasma from the blood banks and have the plasma fractionated by contract after tender, before selling the products back for cost recovery. The small blood banks could produce plasma for products for the Norwegian market, while surplus products from the larger blood banks which are certified for delivery of plasma for fractionation of products to be consumed in the European Community, could be sold on the international market.

Abbreviations: HIV: human immunodeficiency virus; HAV: hepatitis A virus; HCV: hepatitis C virus; SD: solvent detergent

Keywords: Blood; Plasma; Plasma fractionation; Self-sufficiency; Factor VIII; IVIgG; SD-plasma; Octaplas®; Uniplas®

1. Introduction

Norway is a sparsely populated country with 4.5 million inhabitants. Blood donation is voluntary and non-remunerated, and all blood banks are

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hospital-associated. Self-sufficiency has been a national goal since 1980. Norwegian blood banks produce 50–60 tons of plasma per year, of which approximately 90% has been recovered plasma. This is not enough to establish a fractionation plant. The plasma is collected in more than 50 different blood banks, making each individual blood bank commercially uninteresting to the international plasma fractionation industry. At the same time there is a demand for safe blood products.

In the first part of the 1980s, the policy of self-sufficiency and use of cryoprecipitates and factor XI prepared from small plasma pools ensured a high quality of life for Norwegian haemophiliacs and secured a prevalence of anti-HIV of only 6% for the whole haemophilia population [1]. Because of the human immunodeficiency virus (HIV) epidemic, the Norwegian Health Authorities decided in 1985 that plasma, cryoprecipitate and factor IX should be replaced by virus inactivated plasma products prepared from Norwegian plasma by 1988. A pilot project for contract fractionation was initiated by the Red Cross and National Hospital Blood Centre in 1986. After an increasing number of blood banks joined the project during 1987–88, the Norwegian Plasma Fractionation Project was established and took over co-ordination of contract fractionation as of January 1989. The contract fractionation initiative, the postponement of elective orthopedic surgery in haemophiliacs, and a special grant by the Norwegian Parliament for equipment for freezing and storage of plasma, enabled the transition to virally inactivated plasma products with the retention of self-sufficiency [2].

The Project collects plasma from all blood banks in the country. Based on tenders on the European market, Octapharma AG (Lachen, Switzerland) has fractionated and/or virus inactivated the plasma since 1988 according to contract. On behalf of the blood banks and the Norwegian counties, the National Institute of Health issued tenders and was the formal contract partner in relation to Octapharma. With respect to the Project, the Blood Bank Council (appointed by the Directorate of Health) was the professional adviser to the Institute. Production has been carried out at Octapharma's plant in Vienna, Austria, except for the first eight months of 1989 and test fractionation in 1988, when the fractionation was performed at CRTS in Lille, France. All the fractionation products from the fractionation are returned to Norway.

2. Logistics

As each blood bank is small, the time for collecting one full individual batch of plasma for fractionation would be long. The Project ensures that fresh frozen plasma (FFP) is shipped from several blood banks at a time, hence reducing storage time before fractionation. The Project also stores the returned fractionated products. Each blood bank orders from this store, when needed, ensuring that the oldest products are used first. Most of the coagulation factors are sold to the National Institute of Haemophilia and Rikshospitalet University Hospital. Factor VIII is made from all of the plasma. Also, until recently albumin has been made from all of the plasma. The Project ensures that enough, but not too much, of other plasma products are produced. Initially this was factor IX and prothrombin complex (factors II, VII, IX and X). Later, intravenous immunoglobulin (IVIgG) and solvent detergent (SD) treated plasma and cryoprecipitate were introduced.

3. Quality

The Project helped to improve the quality of the blood banks and the plasma. In order to secure high yields of factor VIII, product quality became a point of interest for the blood bank community from the start, resulting in standardised procedures being introduced. FFP which amounted to 95% of the plasma, was generally produced by separation of whole blood within 4 h after collection and promptly snap frozen (core temperature <-28 °C within 35 min for 300 ml bags). Norwegian GMP guidelines were written and inspection by pharmacists from the Surgeon General's office were started largely because of this project [3]. ISO certification and accreditation is now the next step for several blood banks. Another issue will be

certification of larger blood banks for delivery of plasma for commercial fractionation of products to be consumed in the European Community.

Virus inactivation by SD treatment has been the standard procedure for the plasma products. Since 1998 an additional step of dry-heat treatment or nanofiltration has been added for the coagulation factors.

Tests for antibodies directed against HIV and hepatitis C virus (HCV) were introduced in Norway promptly after they were commercially available. Due to low HCV prevalence [4], introduction of NAT test for HCV was delayed until April 2000, when a small pool test (24 samples) was introduced for all blood and plasma collections. However, according to European guidelines, Octapharma introduced NAT testing for HCV on all plasma batches from July 1999. The delay in introduction of small pool NAT-testing in Norway led to the loss of products from two batches of plasma (one for fractionation and one for SD-plasma production) due to positive NAT tests for HCV in the final production pools. This demonstrated that small pool testing, even if expensive, is cheaper than losing whole batches of plasma and corresponding products. From April 2000, small pool HCV NAT testing also became a requirement for the release of cellular products. We have not yet introduced donor exclusion of people who have spent time in the UK. This may delay commercialisation further.

4. Research

A research fund of NOK 0.75 million established by the Project, supports scientific activities within transfusion medicine. In addition, Octapharma has sponsored clinical studies, which have been carried out as agreed to with hospital research organisations. These agreements ensure the investigators' rights to publish the study results.

The studies on IVIgG [5–7] and SD-plasma [8–12] have demonstrated good product quality and interesting clinical results. A study performed by us demonstrated that antibodies directed against Parvovirus B19 in SD-plasma, neutralise Parvovirus B19 in the product [10,13]. Out of 25 plasma batches tested, all contained Parvovirus B19 and high amounts of anti-Parvovirus B19 IgG. When analysing patients at risk for Parvovirus B19 infection one out of nine patients transfused with only SD-plasma and 8 out of 14 patients transfused with SD-plasma and cellular components, seroconverted and developed anti-Parvovirus B19 antibody positive status, however none of them developed clinical symptoms of disease.

A study on fractionated albumin [14] demonstrates blocking of transport sites on albumin due to stabilisers added (sodiumcaprylate and acetyltryptophan) during pasteurisation of the product, while albumin in SD-plasma is not affected. These transport sites are essential for the binding to albumin of such drugs as Naproxen, Warfarin and Digitoxin.

5. New products

A successful clinical study with SD-plasma was performed at the Rikshospitalet, University Hospital, in 1992 [8]. In 1993, Norway was the first country to introduce SD-plasma as the sole plasma for transfusion. The documentation for Methylene blue treatment of plasma was evaluated as insufficient in 1992.

The Octapharma production method for SD-plasma (Octaplas®) differs from the method applied by Vitex in the US for Plas® + SD. Two major differences for Octaplas® are a smaller batch size (200–380 l versus 600–1500 l) and that a final ultrafiltration/concentration step performed by Vitex is omitted. In addition stabilisation of coagulation factors and final citrate concentration differs for the two products. Pool size increases the process time, which can affect labile proteins and loss of activity due to absorbtion, while ultrafiltration could influence the good haemostatic balance observed between the coagulation factors and coagulation inhibitors in Octaplas® [15]. This may explain problems recently observed with Plas® + SD and not with Octaplas®. In addition α2-antiplasmin activity has been reported lacking in the US produced SD-plasma [16] while it is reduced at the most by 76% in Octaplas [15,17–20]. Because α2-antiplasmin is a liver synthesised acute phase serine protease inhibitor of plasmin [21], this

could result in fibrinolysis in patients with severe liver failure. It should therefore be considered to administrate serine protease inhibitor (i.e. Aprotinin) when transfusing Octaplas® to patients with severe liver failure (including liver transplants) or with high risk of fibrinolysis. Due to the ultrafiltration/concentration process the concentration of plasma proteins is in general unchanged in the US produced SD-plasma, while a 10% decrease is observed in Octaplas [17–20].

After SD-plasma was introduced in Norway, the number of units consumed has increased by 78% to 7.9 units/1000 inhabitants. However, the introduction of SD-plasma reduced the unit volume from 270 to 200 ml, thus the consumed FFP volume increased by only 24%.

Norway has been actively involved in the development and clinical testing of an universal SD-plasma (Uniplas®) which can be transfused irrespective of a patients ABO type. In a prospective, randomised study which recently was concluded at Rikshospitalet University Hospital, Uniplas® was found to be efficient, well tolerated and safe [11,12].

A SD treated cryoprecipitate has been produced by Octapharma for use in Norway in the very few von Willebrand factor (vWF) deficient patients not responding adequately to the standard factor VIII product (Octa V.I.®, Octavi® and Octanate®). These are products with a high content of vWF. The SD treated cryoprecipitate also represents a Factor I (fibrinogen) source.

6. Clinical experience

The coagulation factor concentrates are well tolerated and the haemophilia patients have expressed satisfaction with the introduction of highly purified factor VIII and IX concentrates which are easier to dissolve and cause less side-effects than low purity concentrates or cryoprecipitate. Only 10% of the patients with a severe deficit of factor VIII have developed an inhibitor to factor VIII (A. Glomstein, personal communication). Due to a high content of vWF, the factor VIII concentrates have also given satisfactory treatment results in most vWF-deficient patients.

All haemophilia patients are regularly tested for viral disease transmission. For enveloped viruses, which are inactivated by SD the treatment, only one seroconversion for HCV has been observed. No other patients treated with products from the same batches seroconverted, nor were any irregularities found with the batches. The conclusion was therefore that the seroconversion was not related to coagulation factor treatment. With respect to transmission of non-enveloped viruses, which are not affected by SD treatment, four haemophilia patients were infected with hepatitis A virus (HAV) by highly purified factor VIII in 1998. The batch involved in the HAV transmissions was shown to contain plasma from a donor with viremia in connection with HAV infection. We have not observed any HAV transmission with cryoprecipitate or intermediate purity factor VIII concentrates [21], but it is documented that the content of antibodies against HAV is too low in the highly purified factor VIII to neutralise the HAV [13,22,23]. As a consequence, double viral inactivation has since been introduced for all purified coagulation factors and no further viral transmissions have been observed.

Since 1993 the SD-plasma, Octpaplas®, has replaced FFP and other plasma for transfusion in Norway. More than 250,000 units have been transfused to all types of patients, including neonates and 208 liver transplants. Aprotinin has generally only been used in complicated repeat cardiac surgery and patients with severe liver failure undergoing liver transplantation. Neither transmission of viral disease, nor thrombotic/fibrinolytic complications or TRALI, have been reported, related to the transfusion of Octaplas®. The only serious adverse event reported after Octaplas® transfusion, was due to the misuse of 4 units of Octaplas® as an acute volume substitution. This resulted in cardiac arrest due to a citrate induced rapid fall in ionised calcium in an elderly patient who, however, was successfully resuscitated.

7. Self-sufficiency

The Project has secured Norwegian self-sufficiency. It allowed a smooth transition from cryo-

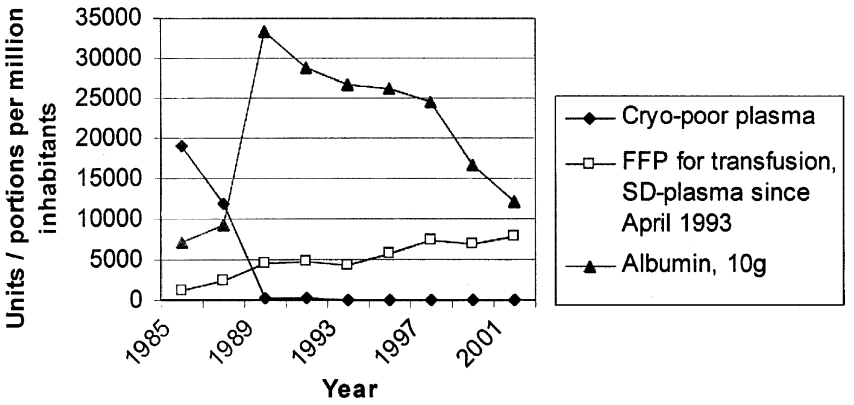

Fig. 1. Plasma and albumin consumption in Norway from 1985–2001.

precipitate and low purity factor XI to high purity products. In addition, self-sufficiency has been established for prothrombin complex (factors II, VII, IX and X), albumin and IVIgG. The amount of factor VIII produced has declined due to the increased purity of factor VIII, double virus inactivation and the reduced plasma volume (and content of factor VIII) caused by the production of A and AB SD-plasma. However, after 1995 a gradual change has taken place in the factor VIII treatment of children with the substitution of plasma derived factor VIII with recombinant factor VIII. This change also prevented a potential product shortage by covering the increased factor VIII needs when treatment in children in the same period was changed from "on demand" administration to prophylactic treatment. This policy change was a major reason for the consumption increase from 2 to 3.5 million IU factor VIII/million inhabitants from 1995 to 2001. However, due to the loss of more than 2 million IU Factor VIII due to positive HCV NAT tests, 2 million IU factor VIII from Swedish plasma were imported to ensure the plasma derived factor VIII supply in 2001. Plasma derived factor VIII is currently primarily used in adult patients with haemophilia-A and von Willebrand disease.

8. Internationalisation and commercialisation

Since the goal of the project was to ensure self-sufficiency, too little focus has been put on the possibility of commercialisation. This is illustrated by the consumption of albumin and IVIgG in Norwegian hospitals. After a peak in 1989, when we used 332.9 kg albumin/million inhabitants, the consumption has constantly declined (Fig. 1). The Cochrane report in 1998 [24] led to a further reduction in albumin use, which in 2001 was only 121.5 kg/million inhabitants. By that time we had a surplus of more than three years production of albumin so, to avoid outdating, Octapharma started to store the albumin paste. The use of IVIgG has been low in Norway and IVIgG was only produced from 30% of our plasma in 2001. Because albumin and, in particular IVIgG, are in short supply on the international market, Octapharma suggested possible sale of surplus albumin and IVIgG outside Norway as early as 1994. This option was included in the contract from 1998, but the Project did not respond to this idea until 2001. The delayed response was partly due to the blood banks resistance to introduce ALT-testing, which was required for commercialisation. Another problem was the lack of certification of the blood banks for delivery of plasma for commercial fractionation of products to be consumed in the European Community.

9. Loss of products

During production, around 0.3% of the plasma has been discarded due to excessive haemolysis or labelling irregularities. Except for three small

batches of factor VIII, which had to be discarded during pilot production in 1988, there have been no product losses due to production errors.

In 1992 three batches of SD-plasma (2580 units) were lost when a trailer sank due to a ferry wreckage. The loss caused a delay of several months in the introduction of SD-plasma in Norway, but due to insurance it did not represent an economic loss to the Project. Since this incident, however, no more than one batch (a month's production) is returned in the same transport.

The major loss of products was due to two plasma batches which tested positive for HCV by NAT in 1999 and to look back procedures. The losses due to look back procedures were increased by the authorities demand to discard products containing plasma collected from a donor one year prior to seroconversion, if the blood bank could not provide samples from the previous donations which demonstrated negative serological and NAT-testing results. This led to a policy of 100% collection and storage of retention samples from every donation as of 2000.

The cost of scrapped products has been divided by the blood banks according to the total amount of plasma delivered to date, and represents NOK 36.5 million (4.6 million (€) or US$) or 2.6% of the total product value.

10. Pricing policy

Prices have been set yearly. The Project has priced its products at, or below, the present international market price for each product. The products have not been subjected to government sales tax.

11. Yield and economy

Over a period of 12 years the project has obtained a high yield of albumin (26.5g/l plasma) and factor VIII (212 IU/l plasma) in addition of securing the Norwegian needs for factor IX, prothrombin complex (factors II, VII, IX and X), SD-cryoprecipitate, IVIgG and SD-plasma.

The Project is based on the fact that the blood bank that produces the plasma pays for the fractionation of this plasma and then owns the products from fractionation. Input–output from the Project is given in Table 1. Over all, the cost of fractionation has been less than the profit from the factor VIII sold by the blood banks to the National Institute of Haemophilia (which has the responsibility for home treatment) or Rikshospitalet University Hospital (where treatment of Norwegian haemophiliacs is centralised). Sale of factor IX, prothrombin complex, SD-treated cryoprecipitate and IVIgG to the same units provided an income of NOK 153 million (19 million € or US$). In addition, the blood banks consumed albumin and SD-plasma worth NOK 461 million (57.5 million € or US$) produced from their own plasma. At the end of 2001, the Project had a stock of coagulation factors, albumin, IVIgG and SD plasma worth NOK 62.1 million (7.8 million € or US$), and paste worth NOK 10.1 million (1.3 million € or US$), based on international spot market prices).

On a national scale this has been a very sound project. Each blood bank has received the products they needed, plus their part of the profit. The profit has been greater than the costs involved. The blood banks could look at it two ways; they could say that the value of each litre of FFP they produced was approximately NOK 1115 (€ or US$ 140), or they could say that the plasma products they used were in fact free of charge. This is most favourable, taking into account that only first class apheresis plasma from licensed blood banks costs € or US$ 80–90 on the international market, and that about 90% of the Norwegian plasma was the less valued recovered plasma. With the reduced consumption of albumin, this is changing. Hospitals using little or no fractionated plasma products pay for fractionation, receive payment for coagulation factors and IVIgG, but have little interest in the albumin they receive. As albumin presently cannot be sold outside Norway, it may appear to be better for the blood bank to sell its FFP to the highest bidder. However, so far no Norwegian blood banks are GMP-certified to deliver plasma for fractionation of products to be consumed in the European Community. For blood banks using

Table 1
The Norwegian Plasma Fractionation Project: plasma income-products outcome 1989–2001

Products	Quantity produced	Value in million US$ or €			
		Total	Scrapped products	Consumed	In stock 31.12.01
Albumin	16,578 kg	51.5	2.7	43.2	5.9[a]
Factor VIII	127,587,896 IU	86.3	1.8	84.4	0.2
Factor IX	19,002,750 IU	7.7	0.2	7.1	0.4
Factor VII	2,399,500 IU[b]	2.0	–	1.3	0.6
SD-cryoprecipitate	538,650 IU[c]	0.3	–	0.3	0.03
IVIgG	380,836 g	9.8	–	8.7	1.1[d]
Octaplas	276,633 units[e]	15.5	0.2	14.4	1.0
Total		172.9	4.6	159.3	9.0
Fractionation costs (include transport, storage and administration)		75.9			
Net result		92.5 (total, subtracted scrapped products)		83.4 (consumed products)	

From a total of 663,638 l of plasma, 599,375 l were fractionated and 64,263 l were used for the production of SD-plasma.
[a] Included albumin paste worth 0.8.
[b] IU Factor VII.
[c] IU Factor VIII.
[d] Included IVIgG paste worth 0.5.
[e] Unit volume 200 ml.

their entire production of albumin, participation in the Project is still very lucrative.

12. Ways forward

As the Project has been a success for the supply of safe blood products based on a self-sufficiency concept and has generated a significant income to the blood banks over a long period, it should not be terminated lightly. At the same time the voices objecting to the present situation need to be heard, since the project is based on all blood banks sharing common interests. One way forward may be to change the role of the Project, from that of a co-ordinator, to a national plasma handling unit. This unit could then buy the plasma from the blood banks and have the plasma fractionated by contract after tender, before selling the products back. The small blood banks could produce plasma for products for the Norwegian market, while surplus products from the larger blood banks certified for delivery of plasma for fractionation of products to be consumed in the European Community could be sold on the international market. The price could be calculated to provide cost recovery for the blood banks that supplied FFP, while all surplus products would be sold for the market price. This would ensure continued national self-sufficiency and give excellent results economically both for each blood bank and on a national level.

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