Self Sufficiency In Plasma And Plasma Derived Medicines

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Introduction

The discussion of this topic hinges necessarily on the question "What is self-sufficiency?" It is our experience that the use of this term many times is used to satisfy political rather than clinical needs.

According to the Economics Dictionary Self-sufficiency means: "the ability of a household or a country to exist on products produced by itself without the need to purchase supplies from elsewhere"[1] The question one might ask is whether it is advisable to create a state of national self-sufficiency for plasma protein therapies.

Sufficiency of plasma depends on the clinical demand of plasma protein therapies. An assessment of the factors underpinning demand is a necessary prelude to addressing the topic.

Clinical demand drivers for plasma protein therapies (PPT's)

The plasma industry has progressed through a series of product 'drivers', i.e. products whose clinical demand shaped the volume requirements for collection of plasma. Other products could then be harvested from this volume to a level which satisfied their clinical demand without requiring further collection [2]. In the western economies, this progression has seen albumin, FVIII and immunoglobulin (Ig) succeed each other as the drivers up to the 70's, 90's and the current period respectively. Thus, in the developed world, in general it is the clinical demand for Ig which determines the plasma sufficiency level.

The Ig demand in modern health systems is influenced strongly by the requirements for immune-modulatory treatment of autoimmune disorders, primarily neuropathies, developed as indications for this agent over the past 20 years [3]. The Ig consumption varies greatly across developed countries [4] and this reflects primarily the level to which these conditions have been diagnosed and treated. Less important in modern systems is the level to which immune deficiency (ID) states are diagnosed and treated, as these conditions are generally accepted as uncontroversial indica-

tions for Ig. The immune-modulatory states, however, are still the subject of some controversy in several reimbursement systems, and are underdiagnosed in others. As they gain approval in the market, they assume the status of the largest single indication for Ig in terms of the amount of product consumed.

It must be stated that the general features of the Ig demand landscape vary across borders, and that in some modern countries Ig demand is still low relative to others because of inadequate medical and reimbursement infrastructure for the treatment of ID states. An example of such a country is Germany [5]. A current realistic assessment of clinical demand for Ig is best attained through examining Ig access where it is funded strictly on the basis of approved evidence-based indications. A useful case study in this regard is the Australian system, where a single – government - payer allocates product on the basis of evidence-based clinical guidelines drawn up by an expert body [6]. A strict gate-keeping role for the issue of the product is enforced through the Blood Service. Scrutiny of the actual amounts issued shows that the vast majority of Ig issued is for indications classified as 'Level 1' in the so-called 'EBM Hierarchy [p 52 in reference 5] [7]. Thus the Australian system presents the features of a single payer providing product based on evidence. The current (2009-10) annual consumption of Ig in this system is 120g/1000 population [8]. This number is the result of a system demonstrating commendable transparency in its processes.

On the basis of the need for 120g of Ig/1000 population, some estimates of the required plasma volume in a national environment may be attempted. Although higher yields of Ig are reported [9], the Cohn fractionation process in use in the majority of plants worldwide is unlikely to yield more than 4g/litre [10]. On this basis, simple calculation suggests that, given access to a fractionation capacity, a population can generate 120g from 30L of plasma collected per 1000 population. Using current technology, this volume of plasma should be able to generate 6000 IU of FVIII; i.e. 6 IU per capita of population, which is close to the optimal level calculated if access to product was unrestricted [11]. Similar estimates for other products will confirm that sufficiency in albumin, other coagulation factors, alpha 1 antitrypsin, etc. can be produced from this plasma volume. Hence, the Ig need is shown to be the driver.

Worldwide plasma supply

Table 1 lists the world's top plasma procurement countries (from reference 3). It may be observed that the 30L/1000

population is attained by only 4 countries[1]. These are the countries which have the highest levels of plasmapheresis collection.

Country	Plasma Production litres/ 10^3 population	Donor status
United States	66	Uncompensated & compensated
Austria	56.6	Uncompensated & compensated
Czech Republic	33	Uncompensated & compensated
Germany	31.6	Uncompensated & compensated
Australia	21.5	Uncompensated
Netherlands	18.8	Uncompensated
Denmark	17	Uncompensated
France	16.3	Uncompensated
Sweden	16.1	Uncompensated
Belgium	15.5	Uncompensated

Title1: The countries with the highest levels of plasmapheresis

It should be noted that there is no ensuing relationship with the level of Ig consumption; some countries with high plasma production consume modest amounts of Ig. Conversely, some countries with no or modest plasma production, eg Ireland and Canada, consume large amounts of Ig. Consumption is a function of clinical and reimbursement policies rather than the availability of domestically sourced plasma.

The plasma for fractionation produced by these countries is of two types. Some (domestic plasma) is used for fractionation into product for the domestic market through arrangements between the plasma collector and a single fractionator. This is the situation in eg Australia, Belgium, Denmark, the Netherlands and France, and is related to the 'self-sufficiency' concept practiced in these and other countries. In other countries, the plasma (market plasma) collected is traded as an international commodity by the collectors and is manufactured into products for the international market. This is the case for most of the plasma collected in the top collecting countries. The world supply of plasma products is heavily dependent on these countries and in particular on the large

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volume of plasma produce collected in the United States. In the US, about one million source plasma donors generated twenty two million litres of plasma, representing about 55% of the world supply [4].

Routes to plasma procurement

Plasma for fractionation is generated through two means. Whole blood collected for transfusion may be separated into cellular (red cells, platelets) and plasma components and the plasma used for transfusion or fractionation. This 'recovered' plasma is thus a by-product of whole blood collection, and was initially viewed in many blood bank systems as an ancillary product secondary to the main blood bank components needed for mainstream clinical transfusion purposes. As the amount of blood collected from most blood donors rarely exceeds two units/year [12], the volume of plasma per donor using this route is seldom in excess of 500cc/year, and never more than one litre/donor/year based on mandatory restrictions on blood collection rates.

Apheresis collection is capable of generating considerably higher volumes of source plasma, depending on the regulatory requirements in the country of collection. The most important country, the US, mandates a maximum of two collections weekly, giving a hypothetical collection rate of 104 donations of about 800ml per donor per year [13]. This implies that 83L per year can be collected, but the rate is rarely attained, as shown by the fact that 22 million collections came from 1 million donors in 2010.

The question of the maximum volume permissible through apheresis collection continues to be a controversial one [14], but studies indicate that the levels approved by the US FDA are not harmful to donor health [15]. Levels permitted in the European Union's jurisdiction are considerably lower [16] but do not limit the capacity of the Czech Republic, Germany and Austria to join the US as important plasma producers.

The infrastructure needed for apheresis collection is expensive and this contributes to the preference of some systems to base their plasma access policy on the collection of whole blood. This may be inadvisable. As may be seen from this review, attaining the national collection level required for the Ig 'driver' has only been achieved by those countries with a high level of source collection. Therefore, irrespective of any clinical and reimbursement policies in place, it appears that source collection is a prerequisite for generating the required volumes. A poli-

cy based on plasma recovery from whole blood is fraught with problems, principally the inevitable and eventual wastage of red cells. Assuming a whole blood to red cell concentrate conversion of 95%, which is what is attained in modern and 'plasma-driven' blood systems, the afore specified plasma collection level of 30L/1000 population will result from collection 126 donations/1000 population and packing 120 of them into red cells. No blood system in the world is remotely close to this, and neither does it have to be, given that current clinical needs indicate that 35-40 red cells/1000 population are sufficient. Striving for levels higher than this will inevitably lead to overusage and wastage of red cells. The iron deficiency imposed on, particularly female, whole blood donors [17] adds to the ethical unacceptability of this situation.

Therefore, source collection is essential to meet the clinical needs worldwide. It is clearly desirable to put to good use any plasma, generated as a result of red cell production, for treating normovolemic anaemia. It is likely that this indication covers not more than half of blood collection needs, which also include the treatment of hypovolemic blood loss from trauma, surgery etc. Emerging indications that many of these patient groups may be at risk from the transfusion of stored red cells [18] and may do better with the transfusion of whole blood [19] should give pause to those who continue to advocate for more recovered plasma collection. The example of the Netherlands and Australia which, although still not at the hypothetical plasma sufficiency level, are generating substantial plasma from a mix of recovered and aphaeresis collection, bear examining.

Sufficiency – 'Self' versus 'Global'

The European Directive 89/381 describes that Member States shall take the necessary measures to promote Community self-sufficiency in human blood or human plasma [20]. It is our view that national self-sufficiency in blood and blood components for transfusion purposes makes sense. To apply this concept to plasma derived medicinal therapies is of a different nature. Many times political motives drive the debate rather than scientific and medical need [21].

The United Kingdom followed the principle until the entire UK plasma supply was banned after the enormous development of BSE in that country. From that moment on, US plasma was imported and used to manufacture PPT's in the plant of the national fractionator.

In Japan a Blood Law was introduced

that calls for self-sufficiency of PPT's. In our view this policy suppresses clinical use and we see that, unlike many other developed and comparable countries, the consumption of PPT's is far behind what one would expect for similar populations [22].

Therefore, the question of the optima route to plasma collection is invariably affected by the continuing and vexatious issue imposed through dogmatic demands for 'self-sufficiency' in all blood derived medicines. It is note-worthy that countries claiming and imposing self-sufficiency, i.e. restricting access to non-domestically sourced plasma products, are among the lowest users of therapies. This includes countries with big economies such as Japan and China. Conversely, countries which have abandoned this dogma, such as Canada and Ireland, are high users. Notably, countries such as Australia and the UK, which previously restricted access based on this policy, have seen consumption levels of PPT's rise as the policy was relaxed.

Essentially, wherever self-sufficiency, i.e. restricted importation, is in place, it has resulted in a lack of patient access to treatments. Defining self-sufficiency on the basis of artificially low clinical needs, generally as a result of inadequate clinical care for chronically dependant patients, simply hides the problem. Access to global market of PPT's is essential for meeting these needs. Currently, this market is heavily dependent on the collection and economic policies of a handful of countries. Increasing plasma collection for the purpose of manufacture in other countries will address this imbalance. Regrettably, such an expansion in capacity frequently gets entangled in the 'self-sufficiency' argument, which rapidly transitions to the 'selfishness' insufficiency situation in many countries. All must contribute to global needs.

Where to get the donors?

Also a feature of this issue is the question of donor compensation. As outlined, source collection is the only route to sufficient supply. The levels required have only been attained in systems permitting compensation of the donors for the arduous and time-consuming process of frequent plasmapheresis. Reflecting again on the 'mixed' blood economies of Australia and the Netherlands, it is possible to generate a substantial capacity from uncompensated donors, but the figures – 4.5, 7 and 22 donations/donor in Australia, the Netherlands and the USA respectively - speak for themselves, and support our contention that for the arduous and time consuming process of plasmapheresis, donor compensation is reasonable. The whole issue of the ethics and

motivation of various donor groups is complex [23], and one may wish to include the plight of untreated patient in their considerations, as well as the issue of over collection of 'voluntary' red cells discussed above. Occasional allegations that compensating plasma donors results in a decrease in uncompensated blood collection – a so-called 'crowding out' effect are not supported by evidence [24]. For global sufficiency of all blood derived medicines, both donor groups are required.

Conclusions

As more health care systems attain the sophistication of treating chronic plasma protein deficiencies to the levels supported by clinical evidence, the supply of plasma needed for fractionation will continue to grow. For this to occur in a balanced and optimal fashion, dedicated collection of plasma at its source is necessary. A diversification of plasma collection to include more countries contributing to the global supply is important. The salutary example of the United Kingdom, which lost its plasma supply after the emergence of a new blood borne infectious agent, demonstrates the need to ensure continued access to plasma and the importance of removing barriers to such access.

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