

Issue Summary
Blood Products Advisory Committee Meeting
December 12, 2003
Gaithersburg, MD

Issue : Review of Plasma Collection Nomograms

Background:

Between October 2002, and September 2003, there was an apparent increase in donor fatalities reported to CBER. Following an average of 3-4 fatality reports per year for the previous 10 years, there were 10 fatalities reported in 2002, and 7 reported in 2003. Eleven donors (64.7 %) comprising seven men and four women were donors of Source Plasma. Three men and one woman (23.5%) were Whole Blood donors, and two men (11.8%) were plateletpheresis donors. The average age of the Source Plasma donors was 38 years with a range of 20 to 55. Their average weight was 185 lbs, and average height, 5 ft 8 inches. Eight of the eleven Source Plasma donors (73 %) died from cardiac disease with severe coronary artery disease listed in seven cases and congestive heart failure in one case listed as the cause of death at autopsy.

Few studies have addressed the severe adverse effects of blood donation. Fatalities in Source Plasma donors were highest among the donors discussed above with most fatalities due to cardiac causes (70.5 %) of all donors and (73 %) of Source Plasma donors suggesting that repeated volume loss in these donors could unmask occult cardiac disease. Heavier Source Plasma donors are also over represented in the data set, suggesting that volume loss could be an additional risk factor for coronary disease in these donors.

The present approved nomogram for Source Plasma donation uses the donor's body weight as the single independent variable to decrease the potential for operator error. However, a medium height is assumed for the nomogram and extreme body types, especially short heavier persons have smaller plasma volumes than persons of taller stature. The nomogram could be inaccurate for these donors.

Discussion:

Regulatory requirements limiting the volume and frequency of Whole Blood, Source Plasma, and Platelet Apheresis collections have been put in place as safeguards to donor health (see below)

Historically, the increased number of plasma collection devices with varying capacities for tailoring each collection to the specific donor resulted in the existence of multiple FDA nomograms specifying the maximum volume of plasma to be harvested from each

donor category based upon the device used, gender, height, weight, hematocrit, and in some centers the length of time in process or the number of cycles.

Because multiple equipment types now commonly co-exist in a location, the potential for error due to the application of an inappropriate nomogram became significantly increased and in 1992, the FDA devised a simplified nomogram based upon weight only. Additionally, the safety of frequent, large volume apheresis was discussed at a workshop on Plasma Donation held in June of 1993 by the Blood Products Advisory Committee (BPAC). Although there were no recognized findings of significant health risk, BPAC recommended that epidemiological studies should be done to evaluate abnormalities in long-term plasma donors. Some studies on long-term safety of frequent /large volume apheresis were carried out by the plasma industry. However, interpretation of the results was constrained due to methodological limitations

Current Limits on Whole Blood donation (21 CFR 640.3 (b))

?? Donation no more frequently than once in eight weeks

?? Removal of 15% or less of Blood Volume in a well-hydrated donor.

?? Standard Whole Blood collection for donors weighing a minimum of 110 lbs (50 kg) is 500 mL, adding the amount for test tubes and tubing on the bag = 538 mL

Limits on Source Plasma Donation: (FDA Memorandum November 4, 1992: Volume limits for automated Collection of Source Plasma)

Donation no more frequently than twice per week with a 48-hour interval

?? 110- 149 lbs (50-80 kg) up to 625 mL (625 mL of Plasma) (10% anticoagulant)

?? 150 –174 lbs (70 to 80 kg) up to 750 mL (750 mL of Plasma)

?? 175 lbs up (over 80 kg) up to 880 ml (800 mL of Plasma)

A comparison of the accuracy of the above nomogram with a more detailed nomogram based on gender and estimated body surface area will be provided at the meeting. Current Council of Europe recommendations restrict the maximum annual volume to 15 liters per year amounting to 288 ml per week. The present German national guidelines limit collection to 650 ml of plasma per session and the maximum annual volume to 25 liters per year amounting to about 40 sessions per year. Both recommendations are regardless of gender and body weight.

In addition to the limits on volume and frequency of collection, the following additional donor safeguards are in place:

Whole Blood donors are questioned about their medical history, and measurements are taken of temperature, pulse, and blood pressure. Hemoglobin or hematocrit is also measured at each donation. Donors of Whole Blood and Source Plasma are asked about specific diseases or medical conditions suffered in the past that may affect their health at

the time of donation. However, no specific questions are asked that could point to a history of, or risk factors for cardiac disease.

The medical history is updated at each donation, but is generally abbreviated for frequent donors of Source Plasma. Body weight, temperature, pulse, and blood pressure are determined and hematocrit concentration and total protein measurements are made at each donation. The minimum hematocrit is 38 % and minimum total protein is 6 gms %. A serum protein electrophoresis is done every 4 months for donors of Source Plasma and the pattern is reviewed before the donor can continue in the program. Source Plasma Donors additionally are given initial and annual physical examination during which a more complete medical history is taken.

Charge to the Committee:

Based on the apparent increase in reported fatalities in donors that potentially could be related to excess volumes of collection during apheresis procedures, and /or underlying cardiac disease, the committee is asked to consider the scientific basis for possible recommendations by FDA to revise the Plasma Collection Nomogram and to screen donors for risk of cardiac disease.

Questions for the Committee:

1. Does the committee believe that the apparent increase in donation-related fatalities warrants further investigation?
 - a. If so, please comment on the design of suitable studies.
2. Does the committee think that FDA should revise its currently recommended nomogram for volumes of plasma collection?
 - a. If so, what revisions should FDA consider?
3. Should FDA consider recommending additional medical screening for donors of Whole Blood or Source Plasma to address cardiac risk?
 - a. If so, what questions or tests should be considered?

