NATIONAL HEMOPHILIA FOUNDATION
for all bleeding and clotting disorders

MASAC Recommendation #184

MASAC CONSENSUS STATEMENT REGARDING THE USE OF FRESH FROZEN PLASMA FOR THE IMMEDIATE REVERSAL OF THE ANTICOAGULANT EFFECTS AND/OR BLEEDING COMPLICATIONS ASSOCIATED WITH ORAL VITAMIN K ANTAGONISTS

The following recommendations were approved by the Medical and Scientific Advisory Council (MASAC) on November 15, 2008, and adopted by the NHF Board of Directors on November 16, 2008.

An increasing number of individuals in the USA are developing a need for long term or indefinite oral anticoagulation. Such conditions include atrial fibrillation, mechanical heart valves, and venous thromboembolic disease.

Oral anticoagulated patients are at increased risk to experience minor, major or life threatening hemorrhagic complications which are precipitated and/or exacerbated by this therapy. Well-known reasons for hemorrhagic complications (especially in the elderly) include drug interactions with innumerable medications, dementia, instability of gait, irregularity of nutrition, and multiple confounding medical issues.

Consensus guidelines for the reversal of elevations of the International Normalized Ratio (INR) and for the treatment of hemorrhage in association with oral anticoagulants have been developed, peer reviewed, and published by numerous hematology-based organizations throughout the world. With minor variations there is general consensus among these guidelines as to how these complications should be treated.

The treatment of life-threatening bleeding in association with oral anticoagulation demands rapid reversal. Fresh Frozen Plasma (FFP) is the only product licensed by the United States Food and Drug Administration (FDA) to reverse the bleeding complications and/or laboratory abnormalities produced by oral anticoagulation. The current standard of care in the United States is to administer FFP in combination with Vitamin K_1 for life-threatening bleeding situations, but this approach cannot successfully produce immediate reversal of the INR because of volume constraints (many if not most of these patients have numerous co-morbid conditions which limit the infusion of large volumes of FFP), time needed to thaw the FFP, and ineffectiveness of INR normalization with this modality. It stands to reason, then, that timely treatment for anticoagulated patients requiring urgent diagnostic or life-or limb-saving therapeutic interventions or those who have suffered major or catastrophic bleeding into critical organs cannot be accomplished efficiently and totally reliably with Vitamin K_1 and FFP.

Ansell et al[1]. state in the recently published 8th edition of the American College of Chest Physicians Consensus Guidelines that immediate and full correction of the INR can only be accomplished by the use of clotting factor concentrates which contain vitamin K-dependent clotting factors.

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The consensus guidelines from several nations outside of the USA have recommended Prothrombin Complex Concentrates (PCCs) for the urgent treatment of life-threatening bleeding associated with oral anticoagulants:

1. UK: PCCs for "major bleeding."[2]
2. Australia: PCCs for "clinically significant bleeding or INR greater than 9 without bleeding."[3]
3. Italy: PCCs for "serious bleeding (CNS or Gastrointestinal)."[4]

Many physicians in the USA have administered PCCs for the rapid correction of INRs in urgent clinical scenarios, such as preparation of patients for neurosurgical procedures to treat CNS bleeds (subdural, subarachnoid or brain parenchyma). The literature indicates that such patients should have a fully corrected INR and enter the OR for definitive treatment within 2 hours after arrival in the Emergency Department.[5, 6]

The use of FFP is potentially complicated by the development of life-threatening TRALI, volume overload, and potential transmission of blood-borne pathogens. This is in contrast to PCCs, which are viral attenuated, concentrated into small volumes, and have not been associated with TRALI.

Currently, there are no PCCs readily available for use in the USA which contain coagulation factors II, VII, IX, and X. Hematologists are the most likely medical subspecialists to treat the bleeding complications of these patients, are the most likely medical subspecialists to administer these concentrates, and are the most likely medical subspecialists to understand their pharmacology and potential adverse event profiles, since these same products have been used to prevent and reverse the bleeding complications in individuals with hemophilia B and other rare bleeding disorders involving the vitamin K-dependent clotting factors. Hematologists and Coagulationists in the United States and their advocacy organization, the Hemophilia and Thrombosis Research Society (HTRS), have objected strongly to the current FDA position that the indication of oral anticoagulant reversal cannot be granted to any PCC without "controlled trials" in which FFP is one of the treatment arms. This position promulgates the implicit claim by the FDA that FFP is the present standard of care for urgent reversal of life-threatening bleeding associated with oral anticoagulants.

The members of the Medical and Scientific Advisory Council (MASAC) of the NHF believe that the promotion of FFP as the present standard of care for urgent reversal of life-threatening bleeding associated with oral anticoagulants in the US is outdated and unacceptably dangerous in 2008. Many hematologists and other physicians consider it unethical to continue to insist that ongoing and future trials for reversal and/or prevention of oral anticoagulant-related bleeding and/or laboratory abnormalities include an FFP arm.

Therefore MASAC urges the FDA to immediately reassess their current stance and opinions on this issue and remove the FFP control arms for the oral anticoagulation reversal trials that are either underway or under future consideration. MASAC further urges the expedited approval of PCCs for this indication.

MASAC urges the FDA, pharmaceutical industry members, and physicians to support the establishment of a registry that would allow for longitudinal tracking of the safety and efficacy of PCCs licensed for this indication.

References:

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