The Role of Warfarin Anticoagulation in Pulmonary Hypertension

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Anticoagulation, particularly warfarin, is often used in patients with pulmonary arterial hypertension (PAH). There is evidence that abnormalities of blood coagulation factors contribute to a prothrombotic state in patients with PAH.[1] Warfarin is the most widely prescribed anticoagulant for the prevention and treatment of arterial and venous thromboembolic diseases. Newer medications such as dabigatran or rivaroxaban, which do not require laboratory monitoring, have not been studied in the pulmonary hypertension population.

Warfarin therapy is complicated by a narrow therapeutic range: individuals with international normalized ratio (INR) values <1.8 are at risk for recurrent thromboembolism, while those with INR values >3.5 are at risk for increased bleeding. Additionally, a wide variation in response among individuals is seen, with daily doses ranging from 1 mg to 20 mg to keep a given patient within a target range. Determining the correct dose can be difficult and incorrect doses can lead to significant adverse events, primarily bleeding and thromboembolism, especially during the initiation of warfarin therapy.[2]

The use of warfarin in PAH patients is based largely on a retrospective study from 1984 of 120 patients with what we now classify as idiopathic pulmonary hypertension. There was a short-term survival benefit in the anticoagulated patients vs those who did not receive anticoagulation.[3] Moreover, experts believe that the PAH disease process itself promotes the formation of blood clots within the pulmonary vasculature to further damage the vessels. Thus, based both upon retrospective clinical data and an understanding of the disease biology, anticoagulation is generally recommended for idiopathic PAH patients.

A typical targeted INR level for PAH patients is 1.5-2.5; however, a higher INR level may be required for patients on infusion therapy at low rates and in patients who have concomitant atrial fibrillation. For atrial fibrillation, the INR target is generally 2 and 3, and patients below this target are clearly at risk for stroke. Patients with artificial valves or a known defect in coagulation (like the antiphospholipid antibody syndrome) may have a higher target INR (2.5-3.5). PAH patients undergoing invasive procedures, such as heart catheterization, will require an interruption of anticoagulation, and therefore healthcare providers should have an understanding of the pharmacokinetics of warfarin. The onset of action is 24 to 72 hours, and a maximum level of anticoagulation at a given dose is generally achieved in 5 to 7 days; the duration of effective anticoagulation is usually 2 to 5 days.[4] Warfarin should be stopped approximately 4-5 days prior to the procedure, which allows the INR to return to a near-normal level. Depending on the patient's underlying risk of thromboembolism, low-dose subcutaneous heparin or low molecular weight heparin may be used to prevent thromboembolism while off warfarin. The INR should be measured prior to the procedure to make sure the level has normalized.[5] If necessary, the effect of warfarin (which functions as a vitamin K antagonist) can be reversed by the administration of vitamin K to increase the level of vitamin K–dependent coagulation factors. Vitamin K normalizes the coagulation cascade and the INR measurement thus returns to normal.[6] Vitamin K is available as an oral preparation and can also be given subcutaneously or, for most rapid effect, as an intravenous infusion over 30-60 minutes.

Drug-to-drug interactions are common with warfarin and can potentially cause an increased INR with risk of bleeding (or a lower INR with risk of clotting). Medications that inhibit certain CYP450 enzymes will potentiate warfarin, while medications that are enzyme inducers will antagonize warfarin. Bosentan is a known inducer of the CYP2C9, CYP3A4, and possibly CYP2C19 isoenzyme systems and therefore may decrease the anticoagulant properties of warfarin. The INR should be monitored more frequently when bosentan is initiated, adjusted, or discontinued in patients taking warfarin.[7] In the large clinical trials, bosentan did not have a consistent effect on warfarin anticoagulation, and thus warfarin dose adjustments need to be individualized for a given patient.

Foods rich in vitamin K can also compete directly with warfarin and reduce the patient's effective anticoagulation (with a reduction in the patient's measured INR). Patients should be counseled to avoid eating large amounts of foods rich in vitamin K or, alternatively, to eat consistent amounts of vitamin K–rich foods so that the effect of warfarin will be constant. Cranberry juice and alcoholic beverages can increase the INR by changing warfarin metabolism in the liver. The potential benefits of anticoagulation should be weighed against the risks in certain PAH patient populations. Portopulmonary hypertension patients have an intrinsic coagulopathy and often have esophageal or gastric varices (dilated veins) that bleed spontaneously; thus, these patients are at risk for severe gastrointestinal (GI) bleeding.[8] The use of warfarin in PAH patients with systemic sclerosis has not been established; however, some will have nasal telangiectasias or gastric antral vascular

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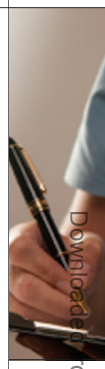

ectasias and thus may be at higher risk of epistaxis or GI bleeding.[9] In patients with chronic thromboembolic pulmonary hypertension, anticoagulation is often recommended as a lifelong treatment to prevent further embolic events.[4] Anticoagulation is generally recommended for PAH patients using miniaturized pumps with very slow infusion rates to prevent clotting of the central line catheter.

Anticoagulation in PAH has not been studied in randomized controlled trials, but has been widely used in idiopathic PAH patients based on small retrospective studies and an understanding of the disease biology. The narrow therapeutic range along with the wide dosing range can make monitoring difficult, and adverse events (including central nervous system bleeding and death) are not uncommon. The potential benefits of anticoagulation should be weighed against the risks, especially when there is an obvious increased risk of bleeding such as in patients with portopulmonary hypertension, those with a history of mucosal bleeding, or those at highest risk for falls. Further research into the role of anticoagulation in PAH is needed to establish best practice recommendations, especially because the risks of warfarin are very clear, while the benefits in individual PAH patients are more difficult to measure.

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