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EDITORIAL

Do We Finally Have a Radiopharmaceutical for Rapid, Specific Imaging of Venous Thrombosis?

It has been known for some time that basing a diagnosis of deep venous thrombosis (DVT) on clinical signs and symptoms is highly unreliable. About half of patients with clinical symptoms suspicious for DVT do not have thrombi (*1*), and about half of patients who actually have thrombi are asymptomatic (*2*). Because anticoagulant therapies are associated with hemorrhagic side effects, it is highly desirable to obtain a reliable diagnosis of DVT before instituting therapy.

Although objective imaging tests for locating thrombi are currently available, they each have limitations. The most widely accepted objective tests for DVT today are contrast venography and B-mode ultrasound (compression ultrasound). Contrast venography is regarded as highly accurate for diagnosing venous thrombi, but it is invasive, painful, requires considerable expertise to perform and interpret properly, and has been associated with a significant incidence of postvenographic phlebitis. It is not suitable for mass screening or repeat studies. Although it has long been regarded as the gold standard, contrast venography is falling out of favor as vascular ultrasound imaging techniques gain in popularity.

In compression ultrasound, a transverse image of major veins is obtained, and pressure is applied with the transducer to attempt to collapse each vein. Incompressibility of a vein is indicative of the presence of thrombus at that location, whereas normal unoccluded veins should be completely collapsed by this procedure. This method and interpretation criteria have been shown to be highly sensitive and specific in the thighs in outpatients (*3*). The accuracy of the test in postsurgical patients has not yet been documented. Compression ultrasound has been shown to be less sensitive for isolated calf vein thrombi (*3,4*); however, a negative study is considered by many to be adequate criteria for withholding anticoagulant therapy (*3,5*). Isolated calf vein thrombi may resolve themselves without anticoagulants and are believed to have a low probability of embolization (*2*). Nevertheless, such thrombi can serve as a basis for propagation to hazardous thrombi in the proximal veins and should be followed until they resolve. A known limitation of compression ultrasound is the incidence of false-positives in patients who have had episodes of prior DVT, possibly because intimal thickening following resolution of a thrombus makes the vein resistent to compression (*6,7*). In addition, performing the test requires a skilled, experienced examiner in order to obtain the best accuracy. Because of the noninvasive nature of the ultrasound exam, it has become highly popular and may become the new standard. For a radionuclide test to be accepted, it will have to offer significant advantages over compression ultrasound. MRI has been proposed as a noninvasive method for locating thrombi with initial success (*8*). However, it is unlikely that this expensive modality, which is in demand for other examinations to the extent that it is booked far in advance, would ultimately be relied upon for mass screening of the lower extremities.

A major limitation of contrast venography and compression ultrasound is that they provide information only about venous morphology. These tests cannot reliably distinguish an acute thrombus from an aged, chronic thrombus. An acute thrombus may be considered as one in which the deposits of fibrin and platelets are exposed

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to the flowing blood and therefore is at risk for further propagation and embolization (*9*). An aged, chronic thrombus that has begun the process of organization, in which vascular endothelium has covered the exposed surface of the thrombus so that it is therefore no longer likely to stimulate platelet activation or cause fibrin deposition, is not of immediate concern for therapy. Nuclear medicine offers the opportunity to evaluate the biochemical state of the lesion: a radiopharmaceutical that can bind specifically to a component of a thrombus would be capable of indicating by its binding whether a thrombus is hematologically active.

DESIGN OF A RADIOPHARMACEUTICAL FOR IMAGING THROMBI

There are two clinical situations in which information about thrombi would be desirable. In the first situation, a patient presents with signs and symptoms suspicious for DVT. It is desirable to know within a few hours whether a thrombus is present so that anticoagulant therapy can be initiated. This test must give accurate results even in the presence of anticoagulants, in order to assess the progress of therapy if required. Prior attempts at specific radiopharmaceuticals for rapid imaging of DVT have been less than successful because the radiopharmaceuticals used, usually labeled fibrinogen or platelets, are not suited to rapid imaging of pre-existing thrombi. These agents inherently have long lifetimes in the blood. Even if one radiolabels these agents with short-lived radionuclides, one will not have a rapid test because the blood background will remain too high for about a day after injection. In addition, these agents bind adequately only to actively forming thrombi. They are relatively insensitive to thrombi whose propagation rate has slowed, such as might be found in patients who come to the hospital after 2–3 days of symptoms. The second clinical situation is the need to screen high risk postoperative patients for the 7–10 days following surgery to detect silent DVT. Although one could perform a rapid test repeatedly during this period, it may be more practical to administer a single dose of a radiopharmaceutical that has both a long lifetime in the blood and a radiolabel that has a physical half-life of several days or more. Images could be acquired periodically for perhaps a week. Iodine-125 fibrinogen has been used as a non-imaging radiopharmaceutical in this setting, and this has been shown to be the optimal setting for the use of ^{111}In-labeled platelets (*10,11*).

The rapid radionuclide test for pre-existing thrombi has presented the greatest challenge. A basic requirement for such a test is a radiopharmaceutical that binds avidly to a pre-existing thrombus and does not require activation by thrombin in order for it to bind to thrombus materials. In addition, the agent should not bind to components of the flowing blood, as this would compete with binding to the thrombus as well as prolonging the residence of the radiolabeled species in the blood, keeping the background elevated for an extended period of time. The two main components of thrombi that may be targeted are fibrin and platelets, but it is important to avoid labeling fibrinogen or circulating platelets in the blood, as both of these have long residence times in the blood pool.

Fibrin is a complex protein polymer which contains a number of antigenically distinct sites to which radiopharmaceuticals could be directed. Many of these sites are not exposed on fibrinogen, the precursor of fibrin which is present in high concentration in the flowing blood. Some of the sites are exposed when thrombin cleaves fibrinopeptides A and B from fibrinogen, resulting in the species known as fibrin monomer, which then spontaneously polymerizes into fibrin strands. Other unique sites are formed during stabilization of the strands or may be exposed during proteolytic digestion of fibrin by plasmin. By identifying compounds that recognize the molecular sites on fibrin which are not found on fibrinogen, a number of excellent possible agents have been identified and are under development. These include monoclonal antibodies which recognize the amino terminus of fibrin (*12–15*), the D domain (crosslink region) of fibrin (*16–19*), and partially digested fibrin (*20,21*). In addition to monoclonal antibodies, certain native human proteins possess affinity for fibrin, including Fragment E_1 (*22–26*) and tissue plasminogen activator (t-PA) (*27–29*).

Platelets deposit in venous thrombi in response to an activating stimulus such as a locally high concentration of thrombin in the vicinity of a fibrin deposit (*9*). Platelets in a thrombus are *activated* platelets as opposed to *resting* platelets that are found in large numbers in the circulating blood. Major changes in the structure of the platelet accompany the transition from the resting to activated state, most notably the fixation of intracellular proteins onto the surface of the cell. This creates molecular sites on the cell surface which did not previously exist on the resting platelet. Examples of compounds that utilize this property are the monoclonal antibodies KC4 (*30*) and S12 (*31–33*), both of which recognize protein complexes of platelet granule origin. Radiotracers based on such antibodies should not bind to resting platelets in the circulating blood, and so a fragment of such antibodies would have fairly rapid disappearance from the blood pool. Other compounds such as synthetic peptides mimicking the molecular recognition units of platelet-binding antibodies are also under development (*34*).

PROSPECTS FOR ^{111}In-C22A Fab AS AN AGENT FOR RAPID IMAGING OF DVT

The monoclonal antibody fragment studied by De Faucal et al. and reported in this issue (*35*) appears to possess most of the required attributes for a relatively rapid test for imaging thrombi: affinity for fibrin, lack of binding to fibrinogen, ability to bind

to thrombi in presence of heparin, and ability to bind to preformed thrombi. The antibody used was C22A, Centocor's designation for antifibrin 59D8, originally developed by Hui et al. (*12*). It recognizes the amino terminus of the beta chain of fibrin, which is exposed when fibrinopeptide B is cleaved from fibrinogen by the action of thrombin. This antibody is nearly identical to T2G1s antifibrin in antigen recognition (*14*) and in its behavior in animal models (*36*). Although the blood disappearance rate of the Fab fragment of C22A is relatively rapid [$t_{1/2}$ = 5.6 hr in dogs (*36*)], the test could probably benefit from faster blood clearance.

In the De Faucal report, there was still significant residual blood-pool activity in the 3-hr images. There is a risk of interpreting images as positive if blood pool is still present. Although in many cases, apparent asymmetry between right and left limbs could be used as an aid in interpretation of images, a false-negative study resulted from misreading bilateral thrombi in the calves. The technique of comparing images acquired at different times is helpful in such a situation: the initial view (10 min postinjection) may show filling defects. At 3 hr, there is likely to be an appearance of uptake at the site of the initial filling defect. At later times, the site of authentic uptake should be even more apparent as the blood background decreases to a negligible level. De Faucal et al. found a significant improvement in accuracy when the images acquired at different times were compared in making a diagnosis, rather than basing the diagnosis on the 3-hr image alone. This antibody probably does not constitute the basis for a true rapid test, as imaging at 18 hr was necessary to raise the accuracy of diagnosis in the last step (from approximately 82% to 92% in the thighs). However, since this late imaging primarily increases the accuracy by eliminating most of the doubtful results, imaging at 18 hr may not be necessary except in about 15%–20% of cases.

The effect of concurrent heparin therapy on the ability of radiolabeled antifibrin antibodies to image thrombi remains a concern. In the De Faucal study, 2/22 proven thrombi were missed in patients on heparin, compared with 3/12 in patients not on heparin, so there was no apparent adverse effect. The results of De Faucal concerning heparin differ from those of other preliminary clinical trials of this antibody (*37*) and are contrary to theory. Heparin would be expected to slow the rate of new fibrin formation and deposition. The epitope recognized by C22A is in the vicinity of a fibrin polymerization site, which in a preformed thrombus is, for the most part, already occupied other molecules of fibrin monomer that have bound. Thus, the potential binding sites for C22A are not exposed in the mid-fibrin strand: the only available sites for binding C22A would be at the ends of the fibrin strands. Thus, the binding of C22A would be expected to be higher in a thrombus which is actively depositing new fibrin, because many more binding sites would be accessible to the C22A, as fibrin monomer forms in the vicinity of the C22A and can bind the antibody as it is depositing. In addition, heparin might alter the patient's thrombotic/thrombolytic balance in favor of fibrinolysis; it has been postulated that this would remove the antigenic sites that are recognized by C22A (*20*). In another clinical trial of ^{111}In-C22A by Jung et al. (*38*), the investigators felt that heparin did not prevent antibody uptake in proven thrombi, but it appeared to have decreased the thrombus-to-background ratio of uptake. In the De Faucal study, no description was given concerning the focality of the uptake during heparin therapy.

With administration of any murine monoclonal antibody, there is concern about the induction of human anti-mouse antibodies (HAMA). This is an issue that should be carefully considered in the context of this test, because imaging of DVT is something that may need to be done repeatedly to assess the course of therapy. Patients with DVT may otherwise have a normal life expectancy so the diagnostic test should be benign. Murine antibody fragments, lacking the Fc portion of the IgG, are expected to have lower immunogenicity and lower risk (*39*). There is still concern, however, that repeated injections of even Fab fragments may eventually result in a significant HAMA titer (*40*). In addition to the concerns about anaphylactic reactions, if a patient has HAMA from prior administration of other murine antibodies for another purpose (e.g., therapy), would those HAMA recognize and bind the diagnostic dose of antifibrin antibody and thus interfere with its targeting? It is hoped that the most promising monoclonal antibodies could be humanized. Alternatively, radiopharmaceuticals based on non-antibody compounds, such as native human proteins Fragment E_1 or t-PA, and those based on much smaller compounds, such as synthetic peptides, may have lower immunogenic risk.

Indium-111-labeled antifibrin antibody C22A is capable of good diagnostic sensitivity and specificity. In the study by De Faucal, 75% of venographically proven thrombi were found by ^{111}In-antifibrin. There were no false-positives, illustrating the benefit of using a thrombus-specific agent. The authors attribute the missed lesions in part to masking of uptake by nearby hot areas of nonspecific uptake (e.g., bladder). In addition, one should recognize that contrast venography cannot distinguish between organized (endothelialized) thrombus and acute thrombus, nor can it distinguish between thrombus and other nonvascular lesions. Thus, in some situations, the antifibrin test may be more accurate than the "gold standard."

In the De Faucal study, the ^{111}In-antifibrin had lower sensitivity in cases of extensive DVT (occlusive thrombosis involving the entire lower limb) than for isolated thrombi. This is an expected problem for radionuclide tests regardless of the tracer employed: how to deliver the tracer to

the thrombus when blood supply to the vessel containing thrombus has been diverted owing to complete blockage? It may be helpful in patients with suspected extensive DVT to administer the radiotracer by pedal injection with tourniquets in place to improve delivery of the radiopharmaceutical to totally occlusive thrombi. Adequate delivery of tracer to occlusive lesions may also be a problem in our goal to reliably image pulmonary emboli with thrombus-avid radiopharmaceuticals.

A ^{99m}Tc label would be preferred over an ^{111}In label for an agent for rapid imaging of DVT. This would provide numerous advantages including lower cost, better availability, higher count rates for a given radiation dose, and better resolution because of the collimators that could be used. The technology now exists for radiolabeling proteins with ^{99m}Tc, and animal studies have indicated that such a radiolabel on an antifibrin fragment can provide diagnostic information equivalent to that provided by ^{111}In-C22A Fab (*36*).

Given radiopharmaceuticals based on molecules such as C22A with high thrombus affinity and specificity, the main factors affecting the success of rapid imaging of thrombi will probably be:

1. The ability to deliver the tracer to the thrombus.
2. Selecting the radiotracer that can find the highest concentration of binding sites exposed on the thrombus.
3. Selecting a tracer that has rapid clearance of blood and muscle background.

Within the next few years, a number of the other new agents should reach the stage of clinical trials and we can see which approach is the most successful. Although the ^{111}In-C22A Fab does not provide quite as rapid a test as would be ideal, the De Faucal report provides encouragement that we are making progress toward the goal of rapid imaging of venous thrombi.

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