HOW GOOD IS D-DIMER?
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The diagnosis of thromboembolic diseases, based on a combination of clinical signs and laboratory values, lacks diagnostic accuracy. Patients with disseminated intravascular coagulation (DIC) and pulmonary thromboembolism (PTE) would benefit from a diagnostic test with accuracy in determining the presence or absence of these disorders. The search for a simple, sensitive and specific test for these hypercoagulable states has led to the development of the D dimer test.

D dimer is produced from degradation of crosslinked fibrin. Each fibrin monomer ends in a D domain. Crosslinking of fibrin monomers by factor XIII results in linkage of 2 D domains. Plasmin is the enzyme responsible for thrombolysis and acts on both fibrinogen and fibrin. The action of plasmin on fibrinogen does not result in the production of d dimer because d dimer is produced only after fibrinogen is converted to fibrin by thrombin and after the fibrin monomers are crosslinked by factor XIII. Plasmin cleaves crosslinked fibrin resulting in a cleavage product consisting of 2 linked D domains or D dimer. Consequently, the presence of d dimer indicates activation of both thrombin (to convert fibrinogen to fibrin) and plasmin (to convert crosslinked fibrin to d dimer).

A logical comparison of tests is between d dimer and fibrin degradation products (FDP), also referred to as fibrin split products (FSP). The presence of FDPs has been used as one of the criteria for the diagnosis of DIC, indicating thrombin activity. FDPs are produced by the action of plasmin on both fibrinogen and fibrin monomer, but not on crosslinked fibrin. In addition to producing d dimer as a cleavage product from crosslinked fibrin, plasmin produces cleavage products D and E as cleavage products of fibrinogen and fibrin monomer. Consequently, the presence of FDPs indicates only the activation of plasmin and not necessarily thrombin.

A portion of the d dimer molecule is antigenic and forms the basis for the laboratory tests to detect its presence. A variety of test methodologies using an antibody against human D dimer have been developed including latex agglutination, red blood cell agglutination, immunoturbidometric assay and enzymatic immunoassay. The agglutination tests are only qualitative or semiquantitative assessments of d dimer but have the advantage of being rapidly and easily performed in a clinical situation. The immunoturbidometric and enzymatic immunoassay (ELISA) are typically the tests performed in reference laboratories since special equipment is required. A latex agglutination assay using an antibody against canine d dimer was briefly available as a point of care test. There is not currently a canine or feline specific test for d dimer.

Human monoclonal antibody tests for d dimer detect canine d dimer. One study reported the latex agglutination assay performed better than the immunoturbidometric assay. Reported reference ranges vary between tests and are approximately 20-390 ng/ml. The latex agglutination test is semiquantitative and <250 ng/ml is considered negative. One limitation of d dimer tests is a lack of standardization between assays from different manufacturers.

D dimer is highly sensitive for the diagnosis of thromboembolic disease, but is not specific for any particular thromboembolic disorder. If 1000 ng/ml is used as a cutoff point, d dimer was 94% sensitive and 89% specific for the diagnosis of thromboembolic disorders. All dogs in that study, with thromboembolic disease, had elevated levels of d dimer. Dogs with liver disease and systemic hemorrhage also have been shown to have elevated d dimer levels, decreasing the test’s specificity, especially in dogs with multiple concurrent disorders. Therefore a negative d dimer is strongly suggestive of a diagnosis other than thromboembolism.

There is generally a high correlation between d dimer and FSP in dogs with DIC. One study which evaluated FDP and d dimer by latex agglutination in dogs with DIC found all dogs with DIC had a positive test result for either FSP or d dimer. In another study, FSP were not found in dogs with pulmonary or systemic thromboembolism, but d dimer test was positive leading those authors to conclude it was more useful for the diagnosis of thromboembolism. Two studies have evaluated specific diseases known to cause hypercoagulable states: parvovirus enteritis and immune mediated hemolytic anemia. None of the dogs with parvovirus enteritis had detectable d dimer levels despite evidence of thromboembolism. Most dogs with IMHA and evidence of DIC had detectable d dimer levels. Using the canine specific test, normal dogs were found to have undetectable levels of d dimer. Dogs with hemorrhage also had elevated levels of d dimer, but the mean value was lower than that for dogs with DIC.

Based on the available evidence at this time, elevated levels of d dimer should be considered supportive, but not diagnostic for DIC or thromboembolism. Dogs with internal hemorrhage or liver disease and elevated d dimer may or may not have DIC or a thromboembolic disorder. Patients with marked elevation of d dimer should be carefully evaluated for thrombosis. Undetectable levels of d dimer make the diagnosis of thromboembolism highly unlikely. There is no data on d dimer in cats.

SELECTED REFERENCES