Laboratory Evaluation of the Liver

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KEYWORDS

• Hepatic enzymes • Bile acids • Bilirubin • Liver disease • Ammonia

KEY POINTS

- Laboratory tests can be used to determine whether hepatobiliary disease is present, if liver disease is primary or secondary, and to monitor response to therapy or disease progression.
- Chronic (>6 weeks) elevations in serum alanine aminotransferase (ALT) activity warrant further investigation.
- Extrahepatic disease should be ruled out when investigating patients with increased serum liver enzyme activities.
- Patients with normal laboratory tests can still have significant hepatobiliary disease.
- Knowledge of the biologic variation of analytes is important for accurate interpretation of laboratory tests.

INTRODUCTION

Laboratory evaluation of the hepatobiliary system has several objectives that include determining whether hepatobiliary disease is present, determining if liver disease is primary or secondary, determining the definitive type of liver disease, and monitoring response to therapy or disease progression. Reaching a diagnosis of hepatobiliary disease can present a challenge for several reasons. First, clinical signs are often nonspecific, and in some patients, the disease may in fact be subclinical. In addition, the large functional reserve of the liver requires a marked loss of functional hepatic tissue before clinical signs due to liver failure ensue. Rarely is a specific diagnosis possible without the aid of a biopsy. Despite these challenges, laboratory tests play an important role in the recognition and diagnosis of canine and feline hepatobiliary disease. This article reviews laboratory tests commonly used to evaluate the hepatobiliary system and discusses their utility as well as their limitations.

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REFERENCE INTERVALS AND BIOLOGICAL VARIATION

Comprehension of the limitations of diagnostic laboratory testing for hepatobiliary disease is important to avoid misinterpretation of results. Generally, these tests are quantitative assays performed on serum or plasma samples that are measured with a continuous scale. The clinical interpretation of these assays is guided by a reference interval and/or predetermined cutoff value. Reference intervals can be established by various methods, but most commonly comprise the central 95th percentile of a healthy reference population. Thus, values from 5% of this healthy population fall outside the reference interval. Determination of reference intervals varies based on the number of test subjects and the distribution of the data. A minimum of 40 test subjects is required according to guidelines established by the American Society for Veterinary Clinical Pathology.[1] Patients with significant hepatobiliary disease can have normal test results, and healthy patients can have abnormal test results. Not every value outside the reference interval is clinically relevant. To avoid misinterpretation, oftentimes cutoff values are used that trigger a certain diagnosis or response. For example, although a serum alanine aminotransferase (ALT) activity of 125 U/L may be greater than the upper limit of the reference interval, only a value higher than that would trigger further diagnostic testing.

Clinical biochemical parameters can vary due to intrinsic biological heterogeneity within a patient, but also can vary due to analytical imprecision. The magnitude of biological heterogeneity is also variable with some parameters having large changes over time and others being under more stringent homeostatic regulation. Comprehension of the presence and degree of intrinsic biological heterogeneity and determination of critical change values for biochemical parameters measured for assessment of canine and feline patients for possible hepatobiliary disease is important. A recent study in healthy dogs found that the critical change value for alanine transaminase was 47.7%.[2] Therefore, in a healthy dog, the alanine transaminase activity must change by at least 47.7% in order for that change to be considered statistically different. The biological variation that occurs in dogs with hepatobiliary disease and in healthy or diseased cats is currently unknown.

SERUM BIOMARKERS OF HEPATOBILIARY DISEASE

The specific laboratory tests used for the evaluation of patients with hepatobiliary disease can be classified into 3 groups: markers of hepatocellular damage, markers of cholestasis, and tests of various liver functions (uptake, conjugation, secretion, and synthesis).

Markers of Hepatocellular Damage

Alanine aminotransferase

ALT is found in high concentrations within the cytoplasm and mitochondria of canine and feline hepatocytes. The serum activity of this enzyme is used as a marker of hepatocellular injury in dogs and cats, and it is considered to be the gold-standard marker for hepatocellular injury.[3] Hepatocytes that are rapidly and irreversibly damaged release their cytoplasmic contents, including ALT, into the extracellular space from where it can enter the circulation. ALT release can also occur following reversible hepatocellular injury, which is thought to occur by cytoplasmic blebbing.[4] Distinguishing between irreversible and reversible damage is not possible based on assessment of serum or plasma ALT activity alone. However, reversible or less extensive injury is generally associated with changes of smaller magnitude than irreversible or widespread cellular injury.[5] ALT is predominantly found in the liver with lower