Proceedings of the 33rd World Small Animal Veterinary Congress

Dublin, Ireland - 2008

Next WSAVA Congress:

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Diagnos Tics f o r T h e e v a l u aTi o n o f T h e l i v e r
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Introduction
Clinical signs of gastrointestinal disease, such as vomiting and diarrhea are extremely common in small animal patients. When seeking advice from a veterinarian, pet owners expect accurate diagnosis and definitive therapy of the problem. In very few cases the diagnosis can be made by history and physical examination alone, but in most cases the veterinarian has to utilize diagnostic tests to arrive at the diagnosis. The challenge for the veterinarian is to choose the most appropriate diagnostic test to arrive at the most accurate diagnosis.

Serum chemistry profile
Serum activities of hepatic enzymes are analyzed as markers for hepatobiliary disease in both dogs and cats. Unfortunately, some of these enzymes are also synthesized in other tissues. Therefore, elevations of serum activities of hepatic enzymes outside the control range can be seen with many non-hepatic conditions. Alanine amino transferase (ALT) is a cytosolic enzyme of hepatocytes and leaks into the vascular space during hepatocellular damage. The serum half-life for ALT is rather short (1-2 days). Mild elevations of serum ALT activities are considered non-specific for hepatocellular injury but moderate to severe elevations are cause for concern and should prompt immediate further work-up of the patient for possible hepatobiliary disease. Alkaline phosphatase shows species-specific differences. In the dog, elevated serum ALP activities are most commonly due to hyperadrenocorticism, iatrogenic drug therapy (glucocorticoids, phenobarbital, or other), or biliary disease. However, primary hepatic disease can also be associated with elevations of serum ALP activities. In cats, serum ALP activities are more specific for hepatobiliary disease.

Gamma glutamyl transferase is also non-specific for liver disease in dogs and cats but is more sensitive for liver disease in cats than it is in dogs. Serum blood urea nitrogen, serum cholesterol, and serum albumin concentrations can all be decreased in dogs and cats with hepatic failure. However, these findings are rather insensitive and are also not specific for hepatic failure.

Serum or plasma ammonia concentration
Plasma ammonia concentration can be used as a crude indicator for the presence of hepatic encephalopathy. The serum or plasma sample must be placed on ice immediately after collection and needs to be analyzed rapidly. However, a plasma ammonia concentration within the reference range does not exclude hepatic encephalopathy as many other substances have been implicated in the pathogenesis of this condition. Some clinicians have recommended the use of an ammonia tolerance test. However, the author does not believe that an ammonia tolerance test yields any further information compared with pre- and postprandial serum bile acid concentrations.

Also, a recent study has suggested that the measurement of plasma ammonia concentration is superior to serum bile acids concentrations for the diagnosis of portosystemic shunts in dogs.(1)

Serum bile acid concentrations
Bile acids are metabolites of cholesterol degradation. They are formed and conjugated in the liver and secreted in the bile. After a meal cholecystokinin stimulates gall bladder contraction and release of bile into the duodenum. Conjugated bile acids play a crucial role in fat absorption as they help to emulsify fat. Conjugated bile acids are re-absorbed in the ileum, reach the vascular space, and are extracted from the portal blood by the liver.

Pre- and postprandial serum bile acids concentrations are used for the diagnosis of hepatic impairment and portosystemic shunting. Food is withheld from the patient for 12 hours and a serum sample is collected. A small amount of food, rich in fat, is fed to stimulate gall bladder contraction and another serum sample is collected 2 hours later. When hepatic function is significantly impaired, extraction of bile acids from the portal blood becomes less efficient and both pre- and postprandial serum bile acids concentrations increase. In patients with portosystemic vascular anomalies pre-prandial bile acid concentrations may be only slightly increased, while post-prandial serum bile acids concentrations are often severely increased. However, the pattern of serum bile acids concentrations is not diagnostic of a specific hepatobiliary disorder and can only suggest the likelihood of one over another disorder.

In some normal patients, paradoxical results are observed in that pre-prandial bile acids concentrations...
are higher than post-prandial concentrations. It has been speculated that this finding is due to gall bladder contraction without food intake. However, it is important to note that this interpretation assumes that both pre- and post-prandial serum bile acids concentrations are below the upper limit of the reference range for post-prandial serum bile acids concentrations. Also, increased pre-prandial bile acids concentrations have been found in dogs with evidence of an altered small intestinal microflora.

Recently, the use of sulfated and non-sulfated urinary bile acid concentrations in dogs and cats with suspected hepatic disease has been described. However, further studies are necessary before their routine use can be suggested instead of serum bile acid concentrations. (2-5)

13C-aminopyrine demethylation blood test
The aminopyrine breath test (ABT) has been shown to be useful in quantifying hepatic microsomal enzyme function in human beings and laboratory animals. Aminopyrine, a compound chemically similar to the non-steroidal anti-inflammatory drugs antipyrine and phenylbutazone, is demethylated by microsomal enzymes in the liver. The liberated methyl groups are oxidized to CO₂, which diffuses into the blood stream, reaches the pulmonary alveoli, and is released into the expiratory air. The administration of aminopyrine labeled with either 13C or 14C isotopes allows for the specific measurement of CO₂ derived from aminopyrine, by detection of CO₂ isotopes released in the expiratory air. Reproducible collection of breath samples can be difficult in veterinary species. Therefore, a 13C-aminopyrine demethylation blood test has been developed and is currently being evaluated in dogs and cats that undergo hepatic biopsy. Initial results have been promising. (6)

Cytology
Cytology can be useful in arriving at a specific diagnosis in patients with a hepatopathy. However, cytology does not allow evaluation of hepatic architecture. Thus, the number of conditions where hepatic cytology is clinically useful is limited to hepatic neoplasia (if cells exfoliate) and hepatic lipidosis.

Liver biopsy
A liver biopsy is the best diagnostic test to arrive at a definitive diagnosis in pets with liver disease. A biopsy can be collected by use of an ultrasound-guided true-cut biopsy, by laparotomy, or by laparoscopy. The advantage of laparoscopy and laparotomy are that bigger pieces can be collected under direct visualization and that complications, such as bleeding, can be identified more rapidly. However, laparoscopy and laparotomy are also more invasive than a true-cut biopsy. No matter what method is chosen, the patient must be carefully evaluated before collection of a hepatic biopsy. This evaluation should include complete blood work, but also a coagulation profile, a platelet count, and a buccal mucosal bleeding time. Multiple biopsies must be taken. One biopsy should be cultured and in dogs a second one should be stored for copper analysis if copper stains suggest copper accumulation in the liver. After a biopsy is collected the patient should be carefully evaluated to identify any potential bleeding. It is important to note that while histopathological evaluation of a liver biopsy can allow a definitive diagnosis of many hepatic diseases, there can be considerable variation in the interpretation of histopathological findings by the pathologist and results should always be considered in light of the clinical picture present.

References