Veterinary Bioscience: Metabolism

WEEK 4 – DRUGS, TOXINS AND TUMOURS

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INTENDED LEARNING OUTCOMES

At the end of these two lectures, you should be able to:

- understand why the liver is the organ most often damaged by toxins
- understand the factors that influence the outcome for an animal that is exposed to a hepatotoxin
- describe the clinical signs, gross necropsy findings and hepatic histological lesions that you might see in an animal that has died shortly after ingestion of a hepatotoxin
- contrast these findings with those you might expect in an animal with chronic hepatotoxicity
- provide examples of toxins that are commonly responsible for acute hepatotoxicity and for chronic hepatotoxicity in domestic animals and name the species of animals most often affected
- understand the mechanism by which alkylating toxins (such as aflatoxins and pyrroles) can induce disease
- understand the factors that predispose sheep to chronic copper toxicity and the consequences of chronic copper accumulation
- recognise the key gross features and indicate the clinical significance of the common hyperplastic and neoplastic processes that involve the liver and/or biliary tree in domestic animals.

KEYWORDS

xenobiotic, phase 1 metabolism, phase 2 metabolism, conjugation, mixed function oxidases, cytochrome 450, predictable hepatotoxicity, idiosyncratic hepatotoxicity, centrilobular necrosis, midzonal necrosis, periportal necrosis, massive necrosis, blue-green algae, paracetamol, indospicine, acute bovine liver disease, mycotoxin, aflatoxin, aflatoxicosis, alkylating toxins, lupinosis, phomopsin, pyrrolizidine alkaloids, megalocytosis, lantana, chronic copper toxicity, neoplasia, metastasis, idiopathic hepatic nodular hyperplasia, cystic mucosal hyperplasia of the gall bladder, hepatocellular adenoma, hepatocellular carcinoma, cholangiocellular adenoma, cholangiocellular carcinoma, carcinoid tumours, haemangiosarcoma, metastatic neoplasia, lymphoma, leukaemia

LECTURES 15 AND 16 – HEPATOTOXINS AND HEPATOBILIARY TUMOURS

The liver is the organ most often injured by exogenous toxins. This in part reflects the fact that ingested toxins are delivered directly to it from the gastrointestinal tract via the portal vein. Some toxins may also be selectively extracted by and concentrated within hepatocytes and/or the biliary system. However, a major reason for the liver's vulnerability to toxic injury is because of the role that hepatocytes play in biotransformation of endogenous substances and xenobiotics.

Hepatic biotransformation is largely performed within the smooth endoplasmic reticulum of hepatocytes by the **mixed function oxidase enzyme system** (cytochrome P450 system). The process is largely designed to convert fat-soluble compounds into water-soluble compounds that can be readily excreted from the body via the bile or urine. Hepatic

biotransformation reactions may generate intermediate molecules that may be more toxic than the parent compound, thereby injuring or killing hepatocytes. Biotransformation also generates reactive oxygen species (free radicals) that may damage cell and organelle membranes.

The most common lesion observed in the liver following acute toxic injury is **periacinar** (zone 3 or centrilobular) **necrosis**. The zonal distribution reflects the fact that the highest activity of mixed function oxidase enzymes is found in the zone 3 hepatocytes.

Several broad toxicological concepts will be introduced in the first of these lectures. We will define predictable and idiosyncratic toxins, discuss the circumstances that predispose to toxicity, and explain the multiple factors (other than the dose of toxin) that influence the consequences of exposure. Drawing on your knowledge of hepatic diseases, we will also compare and contrast the clinical signs, gross necropsy lesions and hepatic histological lesions that can be anticipated in acute and chronic hepatotoxicity in domestic animals.

You will be introduced to a variety of hepatotoxins that commonly cause acute and/or chronic hepatic injury in domestic animals: e.g. blue-green algae, poisonous mushrooms, toxic plants such as lantana, cycads and poison peach, paracetamol, aflatoxins, phomopsins, pyrrolizidine alkaloids, and copper.

In the second lecture, you will be provided with an overview of **hyperplastic** and **neoplastic conditions of the liver and biliary tree**. Many older dogs develop multifocal nodular hyperplasia of their hepatocytes (idiopathic nodular hyperplasia). Although the nodules grossly and histologically resemble the regenerative nodules seen in chronic hepatopathies and cirrhosis, they are never as numerous and the liver is otherwise essentially normal. Such nodules are commonly aspirated or biopsied to allow distinction from genuine neoplasms.

Malignant tumours arising elsewhere in the body commonly metastasise (spread) to the liver. Primary tumours arising in the liver are usually of hepatocellular, cholangiocellular (biliary epithelial) or vascular endothelial origin. We will review the typical gross appearance of these tumour types, their nomenclature, and their expected behaviour in domestic animals.

FURTHER READING

DL Brown, AJ Van Wettere and JM Cullen. Hepatobiliary system and exocrine pancreas. In: JF Zachary (ed.). *Pathologic Basis of Veterinary Disease*. 6th ed., Elsevier, St Louis, Missouri, USA (2017)

JM Cullen and MJ Stalker. Liver and biliary system. In: MG Maxie (ed). *Jubb, Kennedy and Palmer's Pathology of Domestic Animals*. 6th ed., Vol 2. Elsevier, St Louis, Missouri, USA (2016)