Chris Dujardin

Association of Veterinary Anaesthetists
European College of Veterinary Anaesthesia
Spring Meeting 2003

Training Session on

Renal and Hepatic Physiology and Pathology

Anaesthesia in Renal or Hepatic Pathology

Paediatric Anaesthesia

Doorwerth, The Netherlands
27 and 28 May 2003

ECVA Training Days

Program

Tuesday 27th May

9.00 – 13.00: Arrival & Registration

13.30 - 14.30: Hepatic physiology and pathology *R.P. Favier*

14.30 - 15.30: Renal physiology and pathology *A. van Dongen*

15.30 - 16.00: Tea & Coffee

16.00 - 17.30: Anaesthesia in animals with liver and kidney disease
E. Clutton

Wednesday 28th May

9.00 - 10.30: Paediatric anaesthesia *M. Buwalda*

10.30 -11.00: Tea & Coffee

11.00 - 12.15: Anaesthesia and analgesia of paediatric patients, and problems associated with small body size *P. Flecknell*

Hepatic Physiology & Pathology

Robert Favier, Faculty of Veterinary Medicine, Utrecht University, Utrecht, The Netherlands

Functional Anatomy of the Liver

The liver is one of the largest organs in the body weighing around three per cent of the body weight in adults. The left lateral lobe is the largest and this is one reason to take liver biopsies preferentially from this lobe. It depends on the shape of the thorax whether the liver comes within reach when enlarged.

One of the main functions of the liver is detoxification or catabolism of many exogenous and endogenous compounds, most of which are excreted into the bile. The biliary system consists of a tree-like distributed ductular system draining all the hepatic acini. The gallbladder collects only 40% of the bile produced, and the remainder is constantly released into the duodenum through rhythmic relaxations of the sphincter of Oddi.

The blood supply of the liver is both arterial by the hepatic artery and venous by the portal vein. The outflowing blood is collected by the hepatic veins that enter the inferior vena cava near the diaphragm. The total blood flow to the liver accounts for about 20-25% of the cardiac output, 70-80% of which comes through the portal vein. In the fasting state, roughly half of the oxygen supply of the liver is delivered by the portal blood and the other part by the artery. The acinar concept places the portal vein in the centre of the acinus, that is organised around the portal area, and several central veins now called the terminal hepatic veins at the periphery. According to the acinar concept the liver circulatory units are divided into three zones, of which the first around the portal area gets blood with the highest content in oxygen, growth factors and nutrients, and zone three around the terminal veins gets the poorest type of blood.

The liver contains parenchymal cells or hepatocytes (60% in number), endothelial cells, bile duct epithelium, Kupffer cells and fat storing cells. In between the hepatocyte and the sinusoidal cell layers is the perisinusoidal space of Disse. Within the hepatocytes there is heterogeneity with respect to a number of (metabolic) functions. Drug metabolism via the cytochrome P450 mixed function oxidase system seems to be primarily located around the terminal veins.

Liver physiology

The liver has an enormous reserve and regenerative (regulated by growth factors of which insulin is the most important) capacity with respect to most of its functions. The liver plays a key role in many metabolic processes and homeostasis. The liver has also the capacity to store many substances to have them available for the organism when needed. The huge adaptive capacity of the liver as result of reserve mass of liver cells, high regenerative power and metabolic flexibility implies that signs of disease and concomitant dysfunction of the liver often develop after loss of these adaptive capacities to meet the demands of the body.

Pathophysiology Of Clinically Important Syndromes

Cholestasis and icterus

Cholestasis is a reduced flow of bile in the biliary tract. About 60% of the bile is directly released into the duodenum, the rest being stored in the gallbladder. The cause of cholestasis may be localised inside the liver (intrahepatic) or outside in the common bile duct (extrahepatic).

Bile acids are being produced by the liver from cholesterol: the two primary bile acids are cholic acid and chenodeoxycholic acid. Bile acids must be conjugated with glycine and taurine before excretion to make them hydrophilic. The conjugates are actively absorbed in the ileum. All of the reabsorbed bile acids are very efficiently cleared by the liver from the portal blood. Only a small fraction is lost in the enterohepatic circulation that has a cycling

frequency of 10-15 per day. Biochemically cholestasis is detectable by increased plasma concentrations of bile constituents.

The majority of the clinical cases have intrahepatic cholestasis. This form may occur due to leakage of the tight junctions that separate canaliculi from sinusoids or swelling of hepatocytes that occlude the canaliculi in between. In all cases of cholestasis the hepatocytes may become overloaded with substances to be excreted and back diffusion to the perisinusoidal space of Disse is therefore a frequent intrahepatic feature contributing to cholestasis. Extrahepatic causes of cholestasis are relatively rare. In most cases tumours of the pancreas or of the duodenum underlie the obstruction.

Bilirubin, the normal end-product of the catabolism of haem, is the pigment which gives bile its yellow-brown colour. The healthy liver clears bilirubin very effectively from the plasma. Upon conjugation bilirubin is excreted into bile, and the conjugate is not reabsorbed from the intestines. Acholic faeces almost invariably indicates complete extrahepatic bile duct obstruction. It has recently been shown that conjugated bilirubins in plasma bind covalently in an irreversible way to albumin which half-life is about two weeks. After complete recovery from the underlying cholestatic disease, icterus may remain for several weeks

Portal hypertension, ascites, and portosystemic collaterals

Portal hypertension is an abnormally high pressure in the portal circulation. The cause can be prehepatic, intrahepatic, or posthepatic. The most frequent intrahepatic cause of portal hypertension is cirrhosis, followed by chronic hepatitis, lymphoma, fibrosis, neonatal hepatitis and congenital portal vein hypoplasia. The main prehepatic cause of portal hypertension is portal vein thrombosis. Posthepatic causes of portal hypertension may be localised in the inferior vena cava and the heart.

Accumulation of free abdominal fluid (ascites) may result from portal hypertension alone or from the combination of increased portal blood pressure with reduced oncotic pressure due to hypoproteinaemia.

Portosystemic collaterals are nonfunctional blood vessels in the omentum and mesentery. Acquired collateral vessels develops in case of a high pressure gradient between the portal vein and the vena cava and therefore only when the cause is pre- or intrahepatic. The collateral circulation can lead to hepatic encephalopathy.

Hepatic encephalopathy

Hepatic encephalopathy (HE) is a dysfunction of the brain secondary to liver dysfunction. The underlying liver dysfunction is portosystemic collateral circulation, acquired or congenital. HE is a syndrome in which the liver itself albeit diseased is sufficiently functional, but not allowed to exert its role as a guardian in between the intestinal outside world and the rest of the organism. The presence of even complete portosystemic shunting alone is not sufficient to develop HE in most cases; the parenchymal hepatic functions must also be compromised.

The neurological signs in the first stage are aspecific. In advanced cases ataxia, circling, head pressing against a wall, salivation, stupor and coma may be seen.

The pathogenesis of HE is multifactorial and in part not yet elucidated. Chronic HE is a neurotransmitter dysfunction involving several transmitter systems in the brain. The most important neurotransmitter systems involved are the glutamate, the dopamine/noradrenaline and the gamma-aminobutyric acid and benzodiazepine (GABA/BZ) pathways.

For understanding of clinical complications in ammonia metabolism it is important to appreciate that only the molecular, non-ionised form (NH_3) passes cell membranes easily whereas NH_4^+ does not. Hypokalemia is a serious risk factor: low plasma potassium is replenished by exchange of intracellular potassium against sodium and hydrogen; the hydrogen shift induces an extracellular alkalosis and intracellular acidosis. Ammonia penetrates the cell membrane easily but intracellularly it becomes ionised and cannot leave the cell. The increased GABA/BZ receptor tone in HE makes these patients unsuitable candidates for anaesthesia with benzodiazepines and barbiturates.

In case of HE treat the underlying disease. As symptomatically treatment protein restriction and lactulose may be helpful.

Blood Coagulopathy in Liver Disease

Normal blood coagulation occurs via the intrinsic and the extrinsic pathways. All of the clotting factors except the Von Willebrand subtype of factor VIII are being synthesised in the liver. The activation of factors II, VII, IX and X depends on the availability of vitamin K. Biochemically, in liver disease, the extrinsic and intrinsic clotting times may be slightly prolonged due to insufficient protein synthesis or vitamin K deficiency (reduced fat absorption). The only way in which coagulopathy frequently develops in hepatobiliary diseases is by disseminated intravascular coagulation (DIC). For this reason it is essential to measure blood coagulation, especially plasma fibrinogen, before taking a liver biopsy. Fibrinogen levels below 1 g/l are an absolute contraindication for liver biopsy. Once the disease causing hepatocellular necrosis is being treated, the DIC disappears spontaneously.

Laboratory Examination

There are different categories of laboratory parameters measured in blood for the diagnosis of hepatobiliary diseases. They are to be divided into enzyme activities in plasma, bile acid concentrations, serum proteins, blood coagulation tests, ammonia and ammonia tolerance tests.

Enzymes in plasma

Enzymes may be released due to necrosis of the cell and all subcellular compartments. The plasma activity is determined by half life and is different for different enzymes in the same sample. High concentration in the cell and long half life in plasma make an enzyme a sensitive indicator for liver damage. Enzymes are not only present in the liver; the liver shares them with some or many other tissues.

Alkaline Phosphatase (AP) occurs primarily in bone, liver, kidney (to the urine), small bowel mucosa (to intestinal lumen), and placenta. Hepatic AP resides primarily in the hepatocytes lining the canaliculi and in bile duct epithelium. The half-time of AP from liver and bone of dogs is about 70 hours. In the absence of skeletal disease increased plasma AP is always of hepatic origin.

Gamma glutamyl transpeptidase (γGT) is very liver specific. It is localized in cell membranes of the bile duct epithelium. In dogs and cats an elevated γGT indicates cholestasis. It appears in blood via release from damaged bile duct epithelium and by back diffusion of γGT-containing bile to the circulation.

Alanine amino transferase (ALT) is very liver specific in dogs and cats. It is localized in the cytoplasm of hepatocytes. In both the dog and the cat ALT is fairly sensitive and specific and thus a good parameter for use in screening for the presence of liver disease.

Bile acids

Bile acids in plasma are a very specific and sensitive parameter to detect disorders of the liver and biliary tract. Unlike the enzymes, bile acids indicate the function rather than the actual cellular damage of the liver and bile system.

Blood examination in the diagnostic screening for hepatobiliary disease

In general, blood examination does not permit the discrimination of one liver disease from another in a single patient. In animals in which hepatobiliary diseases are suspected on the basis of symptoms or clinical findings, measurement of AP + bile acids or ALT + bile acids (or next best: AP ÷ ALT) is sufficient to detect or reject the possibility of such a disease. Increased values should be followed by further procedures (liver biopsy) to diagnose the type of hepatobiliary disease. When hepatic encephalopathy is suspected, measurement of plasma ammonia is the first blood examination.

Other blood examinations

Chronic dysfunction of the liver can cause hypoalbuminemia. In diseases of the liver or bile ducts the blood coagulation may be abnormal usually as a result of DIC, so fibrinogen should be measured before a liver biopsy. An ammonia tolerance test (ATT) is performed in all cases in which the single basal fasting ammonia provides insufficient information.

Renal Physiology and Pathology

Astrid van Dongen, Faculty of Veterinary Medicine, Utrecht University, Utrecht, The Netherlands

Introduction

The prime function of the kidney is to maintain homeostasis, one of the necessities to ensure a successful anaesthesia.

Unfortunately renal dysfunction, due to renal disease or extra renal abnormalities, is encountered quite often in anaesthetic patients. Chronic renal failure is the more common form of renal disease and can occur in dogs and cats of any age but will be found more often in geriatric animals. Acute renal failure is diagnosed not so frequently but it is a notorious and potentially lethal complication in patients that show a decreased renal perfusion (e.g. animals in shock) or secondary to the use of nefrotoxins (e.g. NSAIDS and aminoglycosides). Even in individual with an apparently adequate renal function, sudden deterioration can occur because of extra renal factors such as hypotension, obstruction of, or rupture in the lower urinary tract and/or sub clinical renal disease that was already present.

Renal anatomy

Macroscopically the kidney can be divided in cortex, medulla and pelvis. The functional unit of the kidney is the nephron, consisting of a glomerulus and a tubular system.

The glomerular membrane is formed by an anastomosing capillary network that is lined by the basement membrane (polyanionic proteoglycans), attached to mesangium (microfilamentory cells and a matrix with various elastic microfibrils) and covered by podocytes (epithelial cell bodies with long primary processes and extensive foot processes). The glomerular tuft is enclosed in a pouch-like extension of the tubule: Bowman's capsule.

Glomerular filtration depends on:
- Surface
- Quality
- Pressure

The renal tubule can be subdivided in differently specialized segments: the proximal tubule, loop of Henle, distal tubule and collecting ducts.
The proximal tubule has a prominent brush border on the luminal side (facing the tubular fluid), large mitochondria, leaky tight junctions, and an extensive lysosomal system, allowing for optimal absorption and secretion of water and solutes. The descending part of Henle's loop has aquaporins (I) and is therefore also permeable for water whereas the thin and thick ascending limb is impermeable for water. The cells of the distal tubule as well as the connecting as collecting duct contain a high density of mitochondria but only few microvilli. Their permeability for water is variable per cell type and sensitive to Aldosterone.
H^+ATPase is variably expressed on either the luminal or basolateral (facing the blood) side.

The juxtaglomerular apparatus forms the connective tissue (extraglomerular mesangium) between to the glomerulus (efferent and afferent arteriole with renin producing cells) and its tubular system (macula densa). It is capable of influencing the perfusion rate of its nephron (tubuloglomerular feedback) but also has systemic significance through the production of renin

The renal interstitium (mainly fibroblasts) is comparatively sparse but important as a scaffold frame and it harbours a variable number of cells from the immune system (e.g. macrophages and dendritic cells).

An extensive microvasculature system is essential for maintenance of the renal tissue and function; the renal artery divides into interlob(ul)ar arteries, from these the afferent arterioles that supply the glomerular tufts. Efferent arterioles drain the glomeruli and subsequently form the peritubular capillaries of cortex and medulla and divide again in to vasa recti which will end in the arcuate veins.

Renal physiology

Kidneys are not only important for the maintenance of fluid, electrolyte and acid base balance, they also participate in the endocrine system by being a target organ for hormones (e.g. aldosterone, vasopressin & parathyroid hormone), production of hormones (renin & erythropoietine) and activation of vitamin D.

Glomerular filtration is possible if an appropriate pressure gradient exists between the glomerular capillary lumen and the pressure in Bowman's space. If blood pressure remains between 80 and 180 mm Hg, a stable net ultrafiltration pressure of 10 mm Hg at the afferent end of the capillary can be maintained through selective vasoconstriction of efferent arteriole (sympathetic nerve stimulation and renin → angiotensin II), and/or vasodilatation of afferent arteriole (e.g. nitric oxide, dopamine, bradykinin, and some prostaglandins) or vasoconstriction of the afferent arteriole (noradrenaline, endothelin, thromboxanes, adenosine, extracellular ATP).

The surface and permeability (quality) of the glomerular membrane are also important factors in the equation that summarizes the glomerular filtration rate. Filtration is selective but not absolute. It is largely determined by the basement membrane and based on size (10.000-50.000 Dalton), shape and charge (relatively small but negatively charged molecules are repelled).

During transport the filtered plasma is altered further through secretion and reabsorption. Specialized membrane proteins are involved in the transport of substances in or out the cell. Enormous quantities of water are (passively) reabsorbed predominantly in the proximal tubulus and the descending loop of Henle. To ensure water balance, fine tuning takes place in the collecting duct where antidiuretic hormone can induce increased water permeability through aquaporins.

The (facilitated) diffusion through the tubular membrane is largely generated by means active (ATP-ase) transport of sodium, creating an electrochemical gradient. The bulk of

sodium is reabsorbed in the proximal and distal tubule and via Aldosterone the collecting duct is stimulated to absorb sodium. Other electrolytes such as potassium, chloride, but also sugars and aminoacids are co-transported with or against sodium (e.g. respectively Na^+-sugars or Na^+-K^+ pump).
Luminal H^+ATPase is capable of secreting protons whereas on the basolateral side protons are reabsorbed and bicarbonate is secreted.

When to Anticipate Renal Dysfunction

Clinical signs

Since advanced age and certain breeds such as (Persian) cats, seemed to be predisposed for renal failure, more vigilance is justified in these patients.
Chronic or acute disease (e.g. trauma, vomiting, diarrhoea, cardiac dysfunction) and previous treatments might have lead to hypotension, can induce pre renal azotemia and will render the patient more susceptible for development of acute tubular necrosis.
Clinical signs of renal disease are not specific and they often only become obvious if a substantial amount of renal function is lost. Depending on the location and severity of renal dysfunction, several abnormalities can occur.

Polyuria with subsequent polydipsia can be indicative for loss of concentrating capacity. Muscle atrophy (often interpreted as weight loss) or even (edema) ascites can be observed when proteinuria leads to hypoproteinaemia and loss of colloid osmotic pressure, a phenomena also known under the name "Nephrotic syndrome". Another complication that might arise from this is an increased coaguloability due to loss of another small protein: anti thrombin III. Lung thrombosis should be considered in patients with sudden dyspnoea or inadequate CO2 wash out.

Substantial loss of renal tissue will lead to symptoms also known as "uremic syndrome" and is the result of retention of various metabolites (not only urea but other, probably much more important, end products of protein metabolism, organic acids, electrolytes such as potassium, etc) and increased lifespan of substances that are normally eliminated via renal clearance (endogenous such as gastrin, but also exogenous e.g. anaesthetic drugs). Symptoms can be gastrointestinal, (anorexia, ulceration, vomiting, diarrhoea), neuromuscular (sopor, tremor, ataxia, paresis), hemorrhagic (melena, hematoemisis).

Pale mucous membranes due to anaemia frequently occurs in renal patients for several reasons: deficiency in erythropoietine will result in a non regenerative anaemia which might deteriorate further due to the reduced lifespan of erythrocyts in azotemic patients and because of blood loss secondary to gastrointestinal ulcerations and an increased bleeding tendency due to uremic thrombopathy.

Compensatory mechanisms that occur in a patient with chronic renal failure can result in over stimulation of the renin-angiotensin-aldosteron system and thus sodium retention. As a result peripheral vascular resistance and circulating volume will increase and lead to systemic hypertension.

Laboratory

In view of the anaesthesia, evaluating the homeostasis is of importance to the anaesthetist. Repeated test results during the procedure (but also as follow up) can also be helpful to determine the effect of (symptomatic) therapy.
Urine production: Oligo or anuria are the first signs of an inadequate renal perfusion and glomerular filtration rate and probably of most value to the anaesthetist during a procedure. Specific gravity (s.g.), glucosuria, proteinuria, microscopic examination of the sediment and bacterial culture can be necessary for further identification of the renal disease but are beyond the scope of this lecture

Urea and/or creatinine will only become abnormal with substantial loss of renal function. Hematocriet (packed cell volume) and reticulocyts can give an objective estimate on the severity of (non) regenerative anaemia in cases with pale mucus membranes but recent or ongoing blood loss can not be evaluated. Moreover, clinical signs such as a high pulse and respiration rate are better criteria to help decide whether or not to administer a (blood) transfusion. Total protein and albumin or electrophoresis, and electrolytes such as potassium, sodium, calcium and of course (blood gasses and) pH can be relevant during an anaesthetic procedure.

Additional diagnostics

Radiographs, ultrasonography, cytology (fine needle biopsy) or histology (true cut biopsy) and function test such as urinary clearance can be needed for a thorough work up of the renal patient but are not necessary to identify an anaesthetic risk factor.

Anaesthesia in Animals with Liver and Kidney disease

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Introduction

Liver and renal disease commonly complicates anaesthesia in companion animals. The main challenges with disease in these (and other organ systems) may be categorised:

1) Quantifying organ dysfunction. Haematological testing aimed at quantifying the extent of organ failure (rather than concentrating on the six fundamentally important variables, e.g. PCV, [Hb], TSP, BUN, K^+, glucose) may be expensive and the results confusing and occasionally counterproductive. It may be better to assume that the animal has no organ function and anaesthetize accordingly. Testing is justified if post-operative monitoring is required.

2) Effects of organ dysfunction on drug behaviour and operation. Organ dysfunction may affect drug disposition through direct, and indirect effects, e.g., by altering blood chemistry and cardiovascular function respectively. It may also affect the animal's capacity to cope with other features of operation such as abnormal positioning, PPV, haemorrhage, hypothermia etc.

3) Effects of anaesthetics and surgery on functional organ reserve. Anaesthesia and surgery should not further impair organ function in the perioperative period. This is achieved in three principal ways:

a) Preserving organ blood flow and oxygenation

i) Avoid, atmospheric, tidal, alveolar, haemoglobinaemic, and stagnant hypoxaemia under all circumstances.

ii) Ensure organ perfusion. This necessitates an understanding of the unique features of the organ's circulation, including the effects of sympathetic nervous activity, haemorrhage, specific drugs, PPV, extradural anaesthesia etc.

b) Avoiding drugs or conditions impairing organ function

c) Avoiding drugs causing direct organ toxicity.

4) Providing an anaesthetic based on 1) 2) and 3) that minimises likelihood of intra-operative complications, post-op morbidity and mortality.

Anaesthesia in Renal Disease

1) Renal dysfunction is quantified on the basis of anamnesis, physical examination and in addition to routine haematology, BUN, creatinine, pH & K^+. Urinalysis and urine output is also informative.

2) Renal dysfunction has important effects on drug pharmacokinetic and pharmacodynamics. The kidney is responsible for: a) control of ECF volume & composition; b) synthesis of erythropoietin and vitamin D pre-cursors; and c) excretion of toxins. Renal dysfunction results in: a) unstable circulating volume / tendency to hypovolaemia; b) metabolic acidosis; c) tendency to hyperkalaemia; d) altered mentation / azotaemia / sensitivity to drugs; e) anaemia; f) hepatic dysfunction; g) hypoalbuminaemia; and h) calcium - phosphorus derangements.

3a) Preserving Renal Blood Flow

Minimizing the effects of anaesthesia and surgery on renal function is based on an understanding of renal blood flow. Considering its size in relation to other organs of the body the kidney (0.5% of body mass) receives a high blood flow (approximately 20 - 25%

of cardiac output). Such flow is necessary the high-energy requirements of tubular processes, particularly sodium reabsorption (75% of renal O_2 consumption).

There are two distinguishing features of the renal circulation. First, the mean glomerular capillary pressure is maintained at 45 mm Hg (approximately 20 mm Hg more than other capillary networks in the body) which is necessary for glomerular filtration. Second, autoregulation allows constant blood flow when renal perfusion pressure is altered and occurs in the cortex but not in the medulla. Over a range of systolic arterial pressure from 90 to 180 mm Hg glomerular filtration rate (GFR) parallels RBF. Glomerular filtration ceases when systolic arterial pressure falls below 60 mm Hg. The effects of autoregulation are achieved by changes in resistance in the afferent and efferent arterioles. When arterial pressure decreases, there is relative vasodilatation of the afferent arteriole and vasoconstriction of the efferent arteriole. This results in an increase in the fraction of plasma filtered (filtration fraction) and glomerular filtration is maintained. If arterial pressure increases, vasoconstriction occurs in the afferent arteriole, with the opposite effects on filtration fraction.

Sympathetic nervous system. Increasing sympathetic activity, e.g. in response to shock, preferentially causes vasoconstriction of the afferent artery, thereby reducing renal blood flow. Epinephrine and norepinephrine mimic this effect. Dopamine causes renal vasodilatation at low doses and vasoconstriction at high doses along with a natriuresis and a redistribution of intrarenal flow from the outer to inner cortex.

It is generally regarded that while adequate systemic arterial pressures are required for adequate RBF, this should be the product of increased cardiac output, rather than SVR, as vasoconstriction in afferent arterioles reduces GFR.

Autocoids Renal vessel vasodilators increase renal blood flow and include prostaglandins (PGI_2, PGE_2), nitric oxide, bradykinin and dopamine. Several of these are synthesized within the kidney and, in addition to their effects on total renal blood flow, may alter the

distribution of blood flow between the cortex and the medulla. In normal health, many of these mediators probably have a minimal influence on the regulation of renal blood flow and its distribution. However, in disease or in stress states, e.g., haemorrhage, they may be significant in maintaining adequate renal perfusion. The potentially disastrous effects of administering NSAIDs on renal function in hypotensive animals due to inhibition of prostaglandin synthesis is well recognised.

3b) Avoid further perturbation of renal function

Drugs or conditions that adversely affect the renin-angiotensin aldosterone system (RAAS) and, or ADH release are the most important. Surgical and physiological stressors promote ADH release, water retention and volume overload. Both barbiturates and morphine promotes ADH release, whereas phenothiazines may reduce it (causing the production of dilute urine).

3c) Avoid nephrotoxins

Methoxyflurane administered for prolonged periods produced ADH-resistant polyuric renal failure in people exposed for prolonged (> 6 MAC hours) primary through fluorotoxicosis. Other inhalation agents appear to have little inherent nephrotoxicity.NSAIDs: The potential nephrotoxicity of COX-1 inhibiting non steroidal anti-inflammatory drugs are well appreciated. In human beings, frusemide, and possibly other diuretics, augments the nephrotoxicity of aminoglycoside and cephalosporin antibiotics. Endogenous compounds like myoglobin, haemoglobin and bilirubin also enhance the damage caused by putative nephrotoxins. Some iodinated radiographic dyes are held to be potentially nephrotoxic in people but (as with methoxyflurane) there appears to be no evidence for this in dogs.

Anaesthesia in Liver Disease

1) There is no liver function test that quantifies the degree of liver impairment in the same way that creatinine clearance does for renal function. The liver has: a) multiple functions;

b) massive regenerative capacity; and c) a central role in homeostasis. Hepatic function is tabled below:

2) Despite the widespread metabolic role of the liver (see table below) there are only nine functional aspects of hepatic disease of concern in anaesthesia.

Function	
Protein metabolism	Synthesis : albumin, acute phase proteins, transport proteins and coagulation proteins. Regulation: amino-acid metabolism. Detoxification of ammonia & synthesis of urea.
Lipid metabolism	Synthesis: fatty acids, cholesterol, triglycerides, ketones. Excretion of cholesterol and bile acids.
Carbohydrate metabolism	Glucose homeostasis (gluconeogenesis, metabolism of insulin & glucagon). Glycogen metabolism & storage.
Vitamin metabolism	Synthesis, storage, activation of vitamins A,B,C,D,E,K
Hormone metabolism	Destruction of polypeptide & steroid hormones
Storage	vitamins, lipids, glycogen, copper, iron, zinc, blood
Digestive function	Bile acid synthesis, regulation & enterohepatic circulation.
Detoxification & excretion	Bilirubin, ammonia, copper, cholesterol, steroid hormones, drugs.

Jaundice. Jaundice can result from increased haemoglobin degradation (haemolysis), obstructive biliary disease (cholestasis) or hepatocellular disease. The anaesthetic problems raised by jaundice are: a) aetiological. Haemolytic jaundice may be associated with reduced CaO_2 while hepatocellular jaundice may be associated with severe liver dysfunction; b) clinical: mucous membrane colour obscurs signs of pallor; c) zoonoses

risk (leptospirosis); d) hepato-renal disorders; secondary renal disorders may arise from pigment toxicity, and, or the original hepatotoxin

Bleeding tendencies. Coagulopathy associated with liver disease has two main components: a) portal venous hypertension which increases venous pressure in splanchnic viscera and in people, produce oesophageal varices which may rupture spontaneously or during inadvertent nasogastric intubation. b) coagulopathies secondary to: i) reduced circulating levels of clotting factors (except VIII); ii) delayed clearance of fibrin degradation products (FDPs) which have anti-coagulant activity; iii) thrombocytopathy; also a feature of hepatic disease.

Hypoalbuminaemia. Has two effects: First, it may lower plasma oncotic pressure and predispose to transudation in the lungs and elsewhere. Second, hypoalbuminaemia decreases the bound : unbound drug ratio and may result in a greater peak intensity of effect for highly protein-bound drugs; over-dose is more likely with thiopentone while toxicity is more likely with NSAIDs. This phenomena becomes real when plasma albumen falls below 25 g L^{-1} All proteins except gamma globulins and clotting factor VIII are produced in the liver. Liver disease and resulting impairment of protein synthesis has three effects: coagulopathy, altered drug kinetics, pseudocholinesterase

Altered pharmacokinetics. Liver dysfunction affects drug disposition in three ways: a) altered protein (albumin) binding; b) altered drug metabolizing ability; c) portosystemic shunting. When hypoalbuminaemia is present, the bound : unbound drug ratio decreases for protein bound drug and may result in a greater peak intensity of effect particularly for highly protein-bound drugs. Altered drug metabolising activity has two components: a) diminution in hepatic blood flow and, or portosystemic shunting; b) deranged enzymatic function. The effects of liver disease on a drug depend on: which of these two derangements are present and the drugs's specific hepatic extraction ratio (HER).

Hepatic extraction ratio is defined as

$$\frac{\text{drug concentration in hepatic vein}}{\text{drug concentration in hepatic portal vein}}$$

Values less than 0.5 reflect high extraction ratios, values greater than 0.5 are low . The metabolism of drugs with low hepatic extraction ratios are principally influenced by changes in hepatic enzyme function. Changes, however, are unpredictable because not all pathways are equally affected by liver disease.

For drugs with extensive 'first pass effects' (high HERs) hepatic clearance is primarily limited by hepatic blood flow, not enzyme activity. Reduced hepatic blood flow and, or portsystemic shunting, a feature of some forms of hepatic disease, decreases the clearance of some drugs and prolongs their effect.

Hypoglycaemia. Glucose is stored in the hepatocyte as glycogen. Glycogenolysis releases this back into the circulation. In gluconeogenesis, lactate, glycerol (from fat) and amino acids are converted to glucose. The starved patient of some species may be prone to problems with hypoglycaemia, especially if demand is increased e.g. pregnancy. Animals with liver disease are prone to hypoglycaemia. This may be especially likely if food is withheld pre-operatively. Hypoglycaemia may cause systemic effects such as neuronal damage, immunosuppression, muscle weakness, etc.

Hepatomegaly / Respiratory Disturbance. Enlarged liver size may reduce FRC and limit lung inflation during breathing, predisposing to hypercapnia and, or hypoxia. This is exacerbated by severe ascites and, or pulmonary transudation.

Overt Clinical Signs. Liver dysfunction is associated with non- specific vague signs such as dullness, listlessness, depression, anorexia, chronic vomiting, diarrhoea and

weight loss. Severe disease may show more specific signs of hepatic encephalopathy. Mildly affected cases may reveal nothing more specific than gastrointestinal disorders (with associated problems) but advanced cases show more typical signs including icterus, cachexia, ascites, neurological disturbances and, in some cases, palpable changes in liver size, shape or consistency. Secondary gastrointestinal disturbances may produces considerations discussed below. Depression is likely to increase the sensitivity to drugs in a non-specific and unpredictable way.

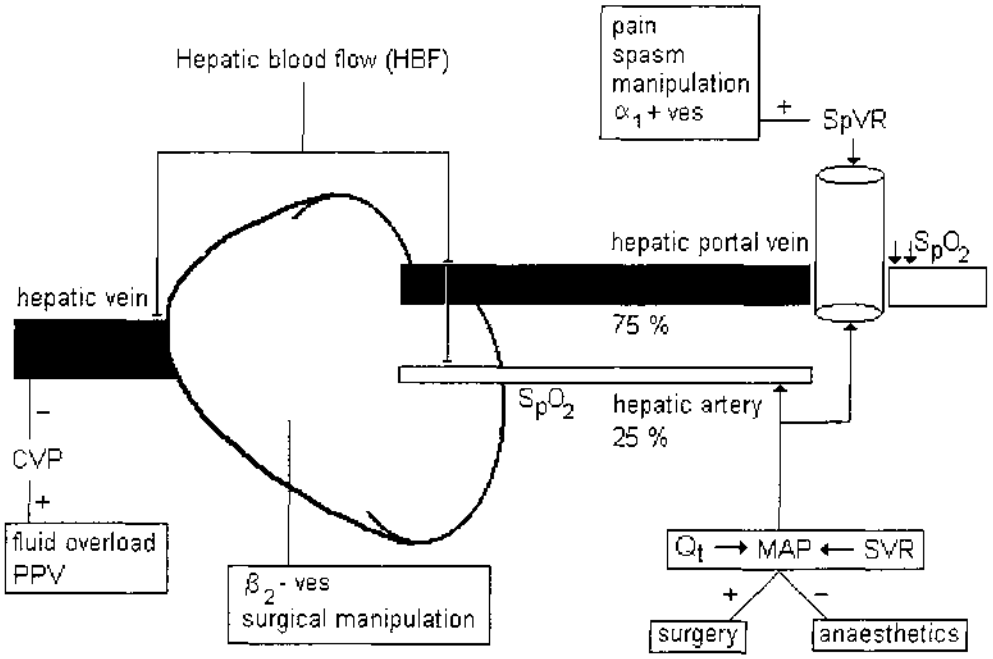
Table 2. Secondary Consequences of Liver Disease

Hepatic encephalopathy	altered sensitivity to sedatives and anaesthetics post-operative neurological complications altered CNS signs during anaesthesia ? Alkalinisation *versus* acidification
Depression	increased sensitivity to anaesthetics
Vomiting / diarrhoea	fluid loss, dehydration, hypovolaemia, electrolyte and pH changes
Cachexia	hypokalaemia, weight loss
Weight loss	predisposition to hypothermia, altered drug distribution

Hypothermia. The high metabolic activity of the liver produces much heat which maintains core temperature. During prolonged laparotomy procedures on animals with compromised thermoregulatory reflexes (extremes of age) for porto-systemic shunt repair, or liver biopsy, there is a very great heat loss.

3a) Preserving Hepatic Blood Flow

The liver receives approximately 25 % cardiac output, but from two independent sources which are influenced by different factors. Only 30 % of hepatic blood flow (HBF) is derived from the hepatic artery; this source is altered by normal factors affecting systemic arterial blood pressure, that is cardiac output and systemic vascular resistance. The remaining 70 % is derived from venous blood draining the intestines in the hepatic portal vein. Blood flow from this source depends on the arterial blood pressure and splanchnic vascular resistance. Thus, hepatic blood flow normally depends on the additive differences between the hepatic artery and hepatic vein, and hepatic portal vein and hepatic vein. Splanchnic nerve stimulation causes splanchnic vasoconstriction and is caused by pain, exogenous catecholamines and hypoxaemia. This lowers hepatic blood flow. Positive pressure ventilation decreases hepatic blood flow by increasing central venous pressure. There is little hepatic autoregulation.



Anaesthetics affect hepatic blood flow primarily by altering arterial blood pressure. Some agents are said to more preserving than others but as a rule, similar lowering of blood pressure whether caused by injectable, volatile or extradural techniques have the same effect on flow. Techniques involving neuromuscular block and positive pressure ventilation reduce hepatic blood flow.

Surgical stimulation and the proximity of the operation are principal determinants of hepatic blood flow. The greatest reductions in man occur when surgery involves the liver itself, e.g. during cholecystectomy.

3c) Hepatotoxins

It is likely that the majority of anaesthetics have been linked with liver-damage in some species at some time, but beyong halothane-associated hepatitis in human beings, little to suggest that toxicity is enhanced when disease is present.

Halothane -associated Hepatitis. Reported in people, predominantly middle-aged, obese. It has been reported in laboratory species of animal, alpaca and possibly goats. It has not been reported in dogs. It provides no grounds to avoid halothane, even in animals with liver disease, and despite other recommendations. That said, isoflurane offers theoretical advantages, and although there are no differences in signs of post-anaesthetic hepatocellular integrity between humans given isoflurane or halothane, isoflurane may be more useful in animals with liver disease. This is because it depresses hepatic blood flow less and maintains hepatic venous oxygen saturation better - not because it undergoes less metabolism.

Fundamentals of Human Pediatric Anesthesiology

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Basic anesthetic techniques are all the same for human adult, pediatric and veterinary anesthesia. Neuronal depolarization, pulmonary ventilation, glucose and oxygen utilization of the individual cell is more or less similar in all mammals. It is the way in how we practice anesthesia that makes the difference. Factors such as body size, shape, weight, organ maturation and a bit of common sense psychology influence the way in how anesthesia is practiced in children (and their pets). The margin of error is smaller and this requires good judgment and constant vigilance. A fluid excess of 100 ml in a neonate compares to 2 liter in an adult! The presentation will review how anesthetic techniques are tailored to the needs of the child.

The Pediatric Anesthesiologist

Pediatric anesthesiology is not yet an official subspecialty. Officially every anesthesiologist is allowed to perform anesthesia in children. However, anesthesia in infants younger then 1 month and complicated cases have to take place in a special pediatric clinic, which usually is a teaching clinic. These pediatric clinics are staffed with anesthesiologists who have dedicated themselves to pediatric anesthesiology. In practice most of the anesthetics given in non teaching clinics concern children > 1 yr. Residents in anesthesiology have a mandatory 3 months rotation in pediatric anesthesiology and are able to do an additional elective of 6 months. Post graduation fellowships (I year) are offered in teaching hospitals.

Anatomical and physiological differences

One of the dogmas in medical training is the phrase "children are not little humans". Fortunately this is wrong, they are! The similarities in anatomy and physiology are overwhelming. There are however important differences that have to be taken in to account when practicing pediatric anesthesiology.

The airway deserves special consideration. Due to a relative big head, large tongue, high glottis and slanting vocal cords it is more difficult to visualize the glottis. The head is positioned in the sniffing position and often some digital depression of the larynx is needed to visualize the cords. The larynx is funnel shaped with its narrowest point at the cricoid level (compared to the vocal cords in adults). This happens to be the level were the cuff of an endotracheal tube is inflated and this can cause a pressure induced edema. This is why tubes without cuff are being used up to 8-10 years of age.

Tidal volume is equal to adults (7 ml/kg) but due to high oxygen consumption (factor 2-3) alveolar ventilation is considerably increased. This is why infants have a high respiratory rate. Relative high alveolar ventilation with a normal FRC results in a quick induction but also a fast desaturation.

Infants have an increased cardiac output (<2 yrs 300 ml/kg/min) compared to adults (75 ml/kg/min). Under the age of two both ventricles are stiff and cannot increase their ejection volume on demand. Cardiac output is frequency dependent and this is why infants have a high heart rate. It also makes them vulnerable to bradycardia. Infants have a relatively increased vagal tone as their sympathic nervous system takes longer to mature. This makes infants sensitive to volatile anesthetics, vagal stimulation and hypoxia. Atropine (0.02 mg/kg) is often given to small infants to counteract this tendency.

The increased body surface/ weight ratio makes infants prone to hypothermia. Pediatric surgeons are used to a hot OR. Body fluids differ considerably, compared to adults infants have more water (73% versus 60% of body weight) and this water is mainly extra cellular 44% versus 20% of body weight. This results in an increased central distribution volume. Also infants have a lower fat content 12% versus 18%. Neonates are obligate sodium losers, their immature kidneys have a low ability to concentrate or dilute urine. At 1 month the kidney is 70% mature.

Pharmacokinetic aspects

Because of the large distribution volume and an increased clearance rate infants need higher doses of propofol and thiopenthal. Although the neuromuscular junction is more sensitive in infants, the dosage of non depolarizing relaxants such as (cis)atracurium, rocuronium and vecuronium is equal for all ages. The increased distribution volume allows for a relative high dose. Under the age of one year vecuronium has a prolonged duration of action due to an immature liver. (Cis) atracurium and rocuronium have a normal duration of action. Under 10 kg of body weight, the dosage of the depolarizing relaxant succinylcholine doubles (2 mg/kg). Succinylcholine is not popular in pediatric anesthesia because of the risk of bradycardia and hyperkalemia. Hyperkalemic cardiac arrest is associated with undiagnosed myopathie (1:250.000).

Age does not affect the dosage of opiates but premature neonates and ex premature infants are more sensitive (probably due to an immature blood brain barrier) and must be monitored for apnea. Risks are bradycardia and chest wall rigidity.

The MAC of volatile anesthetics peaks around 3 months. Neonates have a lower MAC probably due to an immature central nervous system, an immature blood brain barrier and residual progesterone. The increased ratio of alveolar ventilation to FRC results in a more rapid uptake of volatile anesthetics. Other contributing factors are dominant perfusion of the vessel rich group (heart and brain) and an increased cardiac output. The combination of a rapid induction and a lower MAC is dangerous, in neonates it can result in circulatory depression. The risk of myocardial depression is agent selective halothane > isoflurane > sevoflurane.

Anesthetic Techniques

Pre operative

Adults are usually kept nil by mouth from midnight. This will not do in infants. A nil by mouth regimen suitable for children (and adults): > 6 h solid food, > 4h breast milk or non clear fluids, >2 h clear fluids. Sedatives, analgesics and atropine are given as needed 45-60 min before induction rectally or syrup based.

Induction of anaesthesia

When there is no contraindication anesthesia is usually induced in children by mask inhalation. When they are allowed to sit on mother's (or father's) lap and seduced by a strawberry or cherry (you may choose) flavor they usually are willing to breathe through the mask. Sevoflurane in 100% O_2 or in 40% N_2O/60% O_2 is gradually increased from 1 to 8%. When there is loss of eyelid reflex the child is transferred to the table and a vein is cannulated. After administration of a relaxant and an opiate the trachea can be intubated. During the process monitoring is extended from pulse oximetry to ECG, blood pressure and capnography. Short superficial surgical procedures in a healthy child can be managed by spontaneous breathing through a laryngeal mask. In that case relaxation is not necessary. For very short procedures like middle air drainage or the reduction of a simple fracture the child can breath through a mask.

Sick children with a full stomach qualify for a rapid sequence induction (RSI). If time allows the skin on the dorsal side of the hand can be anesthetized with EMLA® cream. After placement of an intravenous cannula the child is denitrogenated with 100% O_2. After the administration of the intravenous anesthetic cricoid pressure is applied to prevent regurgitation of stomach content (Sellick's maneuver). A quick acting relaxant, usually a high dose of rocuronium (1 mg/kg, intubation in 60 sec), is given and the trachea is intubated.

The smallest tube has an internal diameter of 2.5 mm. The average neonate needs a 3.0 or 3.5 tube. Tube size correlates with the base of the nail bed of the 5th digit circumference or can be calculated: (Yrs : 4) + 4

The laryngeal mask is anatomically shaped to fill the hypopharynx with an anterior surface aperture overlying the laryngeal inlet. It was designed to keep an open airway during spontaneous breathing but can be used for positive pressure ventilation as well. It can be used up to 20 cm H_2O positive pressure. There is no reliable prevention of regurgitation of stomach content. The insertion of a laryngeal mask can be done under deep anesthesia without the need of muscular paralysis. Laryngeal masks are sized from neonates to large adults. The laryngeal mask has revolutionized airway management. It has replaced the tube in most uncomplicated day surgery procedures and has earned its place in the difficult airway algorithm.

Ventilator settings must compensate for airway leak (no cuff) and compression volume. To minimize compression volume a pediatric circle system with low compliant tubing is often used. Frequency is age related and decreases from 40/min. in newborns to 15/min. in a 12 yr old. Tidal volume is always 8-10 ml/kg irrespective of age.

Fluid supplementation comprises maintenance, third space loss, blood loss and the correction of preoperative deficit. Solution varies with age: lactated ringers solution and NaCl 0.45%/ glucose 3.3% is used in the average infant but neonates need more glucose: glucose 5%/ NaCl 0.25% or glucose 10%.

All loco regional techniques can be used in children but usually after induction. The sacral canal in children under the age of 7 is filled with loose epidural fat that facilitates the spread of local anesthetic. Caudal and penile blockade are frequently used in day care surgery. The maximum amount of local anesthetic is weight based (3 mg/kg bupivacaine with epinephrine 1:200.000).

Complications

The most frequent complications are laryngospasm, bronchospasm and post extubation croup. Children have sensitive airway reflexes, a high prevalence of upper respiratory tract infections and small airways. As airway resistance is inversely proportional to the 4^{th} power of the radius airway mucosal swelling quickly causes respiratory problems. Post extubation croup is caused by ischemic compression due to a tight fitting tube. It is treated by nebulized epinephrine, corticosteroids and sometimes reintubation is necessary.

A light plane of anesthesia combined with laryngeal irritation (e.g. mucus or blood) triggers laryngospasm. It often occurs when the child is detubated during the excitatory phase of emergence. Gentle positive pressure ventilation with mask and 100% oxygen is usually sufficient but sometimes reintubation is necessary.

Post Operative pain treatment

Oral and rectal analgesics are preferentially given before or just after induction. Rectal acetaminophen is the most frequent used analgesic. Maximum dosage in infants > 1 month and neonates is respectively 100 and 60 mg/kg/day divided in 3-4 doses. NSAIDs are given after the age of 6 months because of renal toxicity.

Morphine is preferably given as a continuous infusion (10-40 mcg/kg/h). Patient controlled analgesia is possible after 4-6 yrs of age. Regional techniques are used as often as possible. An important aspect of post operative pain treatment is the use of a pain scoring system.

Psychological aspects

Children under the age of 6 months do not have separation anxiety. After this age a parent is allowed to accompany the child in to the OR. Preparation is the key for a smooth induction. In the pediatric ward children can play with a facemask and other anesthetic attributes. Special pedagogic nurses help parents and child to cope with anesthesia related uncertainties and anxieties. In most cases this will create a relaxed atmosphere and a co-operative child but sometimes sedatives are necessary (midazolam 0.2-0.3 mg/kg).

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Anaesthesia and Analgesia of Paediatric Patients, and Problems Associated With Small Body Size

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The seminar will deal with both paediatric anaesthesia, and the related issues of anaesthetising very small (but adult) patients. As discussed in the seminar on human paediatric anaesthesia, neonates and infants pose particular problems to the anaesthetist as a result of their immature physiological functions. In addition, there is continued debate concerning the capacity of neonates to experience pain.

Pain perception in the perinatal period

It has been proposed that neonatal and fetal mammals (including humans) lack the capacity to experience pain. The arguments and evidence advanced to support the view that human neonates experience pain parallel those that propose that animals experience pain (Stephens and Anand, 2000). It is simplistic, however, to argue that pain perception will be similar in all species, and it is also reasonable to propose that the capacity to experience pain will develop at different stages in relation to birth in different species. The degree of development of the central nervous system, and the overall level of maturity at birth varies considerably between different mammals, for example rats and mice are relatively immature, with major brain growth occurring post-natally, in contrast to the guinea pig, in which brain growth is largely pre-natal, and the pig, in which the main brain growth phase straddles birth (Dobbing and Sands, 1979). What remains uncertain, however, even in the human fetus, is at what stage pain (rather than nociception) develops.

Although it would clarify many debates concerning animal welfare if the answer to this question could be provided, there are other factors related to pain and stress in the perinatal period that need to be considered. It has been demonstrated in a number of species that

nociceptive responses are well developed in the immediate postnatal period (Anand, 1998, Fitzgerald and Jennings, 1996) and that noxious stimuli can have prolonged effects on neuronal development. Neonates also mount a pronounced metabolic and hormonal stress response to noxious stimuli, and some species show prolonged behavioural changes (Kent et al, 2000). It has also been well established that exposure to stressors of many types in the neonatal period can result in changes in the stress response in later life. Numerous studies aimed at defining the response of neonates to noxious stimuli have demonstrated the positive effects of analgesia and anaesthesia in minimising the undesirable effects outlined earlier. In human neonates, provision of adequate anaesthesia is now widespread, but use of analgesics is still restricted by concerns as to side effects, and a failure to adequately assess the degree of pain experienced by these infants. Similar concerns can restrict analgesic use in perinatal animals, but there are also important practical constraints, and some of these are outlined below.

Selection of anaesthetic agents

The pharmacological effects of a number of anaesthetic agents vary considerably in neonatal animals. The effects can be dramatically different, for example mortality associated with some anaesthetic agents can be high (eg >10%, Danneman and Mandrell, 1997). This has led to the development of some anaesthetic (or immobilising) techniques that, although very safe, may not provide adequate analgesia or anaesthesia. Hypothermia has been widely used as a method of anaesthesia for neonatal rats and mice in research facilities. Animals are immobilised, are unresponsive to surgical stimuli, and may be unconscious. It would appear that no studies of CNS activity have been undertaken in these animals, but it has been argued that since peripheral nerve conduction is slowed or blocked, pain perception is not possible. An additional complication of the technique has been suggested, in that re-warming of cooled tissues is painful in man, and hence although hypothermia may be anaesthetic, it may be followed by pain or discomfort on re-warming. In our laboratory, we found the technique inconvenient for surgical procedures in neonates, and since reliable and safe alternative techniques were available (Danneman and Mandrell,

1997), we chose to use inhalational anaesthetics. When these techniques were not suitable, because of difficulties of anaesthetic delivery, we used a neuroleptanalgesic technique for neurosurgery and found this to be safe and effective (Clowry and Flecknell, 2000). Since effective and safe alternatives to hypothermia are available, it seems reasonable to suggest that they are used, pending more information on the welfare implications of hypothermia as an anaesthetic technique.

Other techniques which give rise to welfare concerns are the use of neuromuscular blocking agents, in conjunction with anaesthetic techniques that are clearly inadequate in the species concerned. These issues mirror those recognised in adult animals, but raise some specific concerns because of differences in anaesthetic sensitivity in neonates. For example, the concentration of volatile anaesthetics needed to produce surgical anaesthesia varies with age, and use of recommendations from adult animals can lead to inadequate anaesthesia. An additional complication is that hypothermia reduces the concentration of anaesthetic required (Satas et al, 1996), and neonates are particularly susceptible to the development of hypothermia during anaesthesia. Careful management of body temperature is thus even more critical in neonates than adults. As in adult animals, assumptions concerning anaesthetic efficacy based on efficacy in man are also made, resulting in potentially ineffective regimens being employed, for example ketamine, either alone or in combination with opioids. There are also, regrettably, examples of neonatal anaesthesia in which, following completion of surgery, immobility was apparently achieved solely with neuromuscular blocking agents (Graham et al, 1996). This practice is questionable in human neonates, and also in animals – in addition, the stress responses discussed earlier may have significant effects on the results of such studies.

Fortunately, since a range of species have been used as animal models for human neonates in studies designed to investigate the efficacy and pharmacokinetic and pharmacodynamic properties of anaesthetic and analgesic agents, there is a steadily increasing database that can be used when developing anaesthetic protocols for this age-group. The species used

are, however, rarely include those that might be anaesthetised in a veterinary clinical situation (dogs, cats and horses).

Anaesthetic management

Aside from the problems of selecting an appropriate anaesthetic, the small size of neonatal animals, and the relative immaturity of some of their organ systems can lead to difficulties on anaesthetic management. In many species, the tissue oxygen demands are two- to three times greater than in adults, and if oxygen is not supplied, then the neonate may develop hypoxia. This may be exacerbated by the narrow diameter of the airway leading to increased resistance and hence increased work of breathing. In addition, a lowered functional residual capacity may lead to progressive alveolar collapse. In larger neonates (eg lambs and piglets), endotracheal intubation and use of intermittent positive pressure ventilation may be advisable, but the pressures used for ventilation must be monitored carefully to avoid damaging the lungs. The cardiovascular system is also less well developed, and changes in cardiac output are produced primarily by changes in heart rate. Drugs such as opioids that can cause bradycardia in some species may therefore produce significant hypotension if used as adjuncts to anaesthesia. Blood loss is also much more likely to cause hypotension than in adults, so great care should be taken to avoid this when carrying out surgery. Renal function may also be less efficient, and neonates are generally less able to tolerate excessive administration of fluids. It is therefore important to measure the total volumes of fluid administered carefully, and to avoid rapid infusions. As mentioned earlier, neonates are particularly sensitive to hypothermia, and this can lead to delayed recovery or to death in the perioperative period. To minimise this problem, the operating area should be warmer than for adults, all fluids should be warmed to body temperature before administration, and if possible, anaesthetic gases should also be warmed and humidified. Insulation and active warming should be commenced as soon as possible during induction of anaesthesia, and continued until the animal is fully recovered.

All of these issues are further complicated by the many practical difficulties of monitoring and managing anaesthesia in small animals. Many of the anaesthetic monitoring devices function effectively only in animals weighing 200g or more, and others function reliably only in even larger individuals (>1kg). Aside from problems associated with low signal strength (eg ECG and respiratory monitors), the higher resting heart rates or respiratory rates may exceed the upper limits of some devices. Measurement of blood pressure is more difficult – most neonates are too small to allow non-invasive monitors to be used, and direct measurement after arterial catheterisation may also be technically difficult because of the small body size. Even catheterisation of peripheral veins for administration of fluids and anaesthetic and emergency drugs can be difficult.

Given all of these potential problems and complications, it is essential that the highest standards of perioperative care are implemented, in order to minimise morbidity and mortality.

Post-surgical analgesia

As with selection of anaesthetics, determining the most effective analgesic regimen for neonatal animals is difficult. It is also important to appreciate that if analgesics are to be used effectively, they should be given at a dose appropriate to the particular individual that requires pain relief. This is only possible if the degree of pain present can be assessed accurately. Such assessments are difficult to make in adult animals (Dobromyskyj et al, 2000) and very limited information is available in relation to many of the common laboratory species. There are extensive studies of acute pain responses in farm animals (Kent et al, 2000), but as yet these have rarely been combined with studies of analgesic efficacy. At present then, analgesic therapy can only be given based on extrapolation from older animals, and from man. Where published data of efficacy in analgesiometric tests in neonates are available, these can be used to modify estimated dose rates (Luks et al, 1998). It is important to emphasise that this approach is highly unlikely to produce optimal analgesic regimens, but is simply the best approach that can be adopted with our current

state of knowledge. The sensitivity, at least to opioid analgesics, varies considerably with age, (Marsh et al 1999) and is likely to be related both to changes in the developing CNS (Alvares and Fitzgerald, 1999) and to factors related to drug metabolism and drug distribution. Information concerning non-steroidal anti-inflammatory drugs is very limited, although data concerning their use in some farm species are available, as carprofen and flunixin, for example, are marketed commercially for use in calves.

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