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ST VINCENT'S PATHOLOGY

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BILIRUBIN INFORMATION SHEET

PHYSIOLOGY

Bilirubin is a tetrapyrrole product of haem catabolism of molecular weight 584. It is formed from haemoglobin (70%) and other haem molecules (30%) by the action of the haem oxygenase and biliverdin reductase. The product, unconjugated bilirubin, is not water soluble and circulates in blood bound to albumin. This form of bilirubin is then taken up by liver and mono- or di-conjugated with glucuronide by the action of UDP glucuronyl transferase. The glucuronide is then transported into the biliary canaliculus against a concentration gradient. This is the rate limiting step in the transport of bilirubin from blood to bile and conjugated bilirubin can leak back from hepatocytes and appear in the bloodstream. In normal individuals less than 5% of plasma bilirubin is conjugated. Conjugated bilirubin is also known as direct bilirubin because it reacts with measuring reagents without an accelerator, total bilirubin measures an accelerator, eg alcohol, in order to include unconjugated bilirubin which is non-polar, and reacts more slowly.

Bilirubin diglucuronide is converted to urobilinogens in the large bowel by the actions of bacterial beta-glucuronidases. Small amounts of urobilinogens are absorbed and re-excreted by the liver. This may be interrupted in liver disease leading to the presence of significant amounts of urobilinogen in the urine. Unconjugated bilirubin is not found in the urine, small amounts of conjugated bilirubin can pass the glomerulus. Conjugated bilirubin in the circulation may bind covalently to albumin, forming delta bilirubin which is removed slowly from the circulation. Clinical jaundice seen at about bilirubin concentrations of 35 to 50 µmol/L and above.

PATHOLOGY

Plasma bilirubin may be increased due to increased production (pre-hepatic causes), hepatocyte dysfunction (hepatic) or cholestasis (post-hepatic).

Pre-Hepatic causes of increased serum bilirubin include haemolysis, ineffective erythropoiesis, transfusion, and haematoma resorption. Levels are rarely >100 µmol/L in the absence of other contributing factors. The bilirubin is likely to be largely of the unconjugated variety.

Hepatic causes may be inherited (eg Criglar Najar, Gilbert's, Dubin Johnson or Rotor syndromes), or secondary to hepatocellular disease (eg infective, autoimmune, toxic, septic, hypoxic). In cases of hepatocellular damage there will also be elevations of ALT and AST. The bilirubin may be conjugated or unconjugated and this test is unhelpful.

Post-Hepatic causes may be intrahepatic (eg primary biliary cirrhosis) or extrahepatic (eg gallstones, tumour, pancreatitis, sclerosing cholangitis). Elevations due to obstruction are

usually associated with elevations of ALP and GGT. An ultrasound is useful in the investigation of these patients.

Blood transfusion may contributary factor in 20% of in-hospital cases, often marked by a rise predominantly in unconjugated bilirubin. Other causes are often co-existent, and this does not necessarily represent incompatible transfusion and may be more common with older blood.

Major trauma is commonly associated with hyperbilirubinemia which may be due to transfusion, shock (affecting liver biliary excretion), and haematoma resorption.

CONJUGATED AND UNCONJUGATED BILIRUBIN

The measurement of the amount of bilirubin which has been conjugated is only occasionally a useful test. If the cause of the elevated bilirubin is uncertain a high percentage of unconjugated bilirubin may suggest a pre-hepatic cause and a low level is consistent with post hepatic causes.

GILBERT SYNDROME (FAMILIAL BENIGN UNCONJUGATED HYPERBILIRUBINAEMIA)

This is the most common inherited cause of hyperbilirubinemia and, as the alternate name suggests, does not cause an increase in mortality or morbidity. The cause is a reduced activity of hepatic bilirubin UDP-transferase, one of the conjugating enzymes, leading to accumulation of unconjugated bilirubin without other evidence of liver disease. Several different mutations in the UGT1A1 gene have been identified. The bilirubin rarely exceeds 80 µmol/L and rises in response to starvation and falls in response to some drugs. Investigation is usually limited to exclusion of other possible causes and measurement of the unconjugated fraction. In rare cases confirmation with genetic testing may be indicated. No treatment other than reassurance is required.

NEONATAL HYPERBILIRUBINAEMIA

PHYSIOLOGICAL JAUNDICE: the average bilirubin in term newborns is 100 µmol/L at 2-4days. The level is usually <20 µmol/L by day 12. The level may be as high as 200 µmol/L in pre-term infants.

PATHOLOGICAL JAUNDICE: This should be considered when the bilirubin >170 µmol/L in term infants or >240 µmol/L in pre-term infants

CAUSES OF PATHOLOGICAL JAUNDICE:

<1 day: Erythroblastosis fetalis
Concealed haemorrhage, haematoma, ecchymoses
Sepsis: CMV, Rubella, Toxoplasmosis
Drugs: vitamin K, novobiocin

<4 days: Transient familial neonatal hyperbilirubinemia (rare)
Sepsis
2-3 days: Crigler Najar Syndrome
Physiological jaundice (most common)
4-7 days: Breastfeeding (1/200)
Sepsis
>7 days: Breastfeeding
Sepsis
Hepatitis
Bile duct atresia
Galactosemia
Hereditary spherocytosis
Thalassaemia, sickle cell disease
Pyruvate Kinase, G6PDase deficiencies

Kernicterus: usually only occurs with bilirubin > 300 µmol/L. More common with prematurity, hypoxia, infection.