Ministry of High Education and Scientific Research

Al-Qadisiyah university

College of pharmacy

Neonatal Hyperbilirubinemia

A Research
Submitted to the College of pharmacy Al-Qadisiyah University
in
Partial Fulfillment of Requirements of B.Sc. Degree of Science in pharmacy

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2017 A.D **1439 A.H**

يَرْفَعِ اللَّهُ الَّذِينَ آَمَنُوا مِنْكُمْ وَالَّذِينَ أُوتُوا الْعِلْمَ دَرَجَاتٍ وَاللَّهُ بِمَا تَعْمَلُونَ خَبِيرٌ ***(11)***

صدق الله العلي العظيم

سورة المجادلة < الآية ١١>

Acknowledgements

First of all thanks God for helping me in performing this work I would like to introduce my deepest thanks to my supervisor Dr.Mohammed Abdul Reda Yassen for his guidance and kindness throughout the study.

I would like to thank the staff of AL-Hussein Hospital for facilitating cases with there clinical history .

I would like to express sincere gratitude to my family especially my mother and my father for there support and help to perform this research in the best way.

I

DEDICATION

To al- imam al Mahdi .

To the big heart my dear father ,To my great mother .

To my brothers and sisters ,To my family .

To the people who paved our way of science and knowledge .

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ABSTRACT

Jaundice is a complex disease. Jaundice is actually the high bilirubin level in the body. Yellowing of skin, mucous membranes and skin are common presentations of jaundice. Jaundice has various variants including pre-hepatic jaundice (due to hemolysis of red blood cells), hepatic jaundice (due to defect in capture, conjugation and excretion of bilirubin by liver) and post hepatic jaundice (due to the obstruction of extra hepatobiliary system). The causes of various variants of Jaundice is either acquired or congenital. High plasma bilirubin level can cause various manifestations involving satiety, gastrointestinal bleeding, diarrhea, anemia, edema, weight-loss and can be fatal because it can cause psychosis, lethargy, seizures, coma or even death. High bilirubin level can help in the diagnosis of Jaundice. Differential diagnosis of various variants of Jaundice can be carried out on the basis of bilirubin level (conjugated and unconjugated), ultrasonography and other radiological techniques. The proper management of Jaundice is high water intake and low fat diet. The primary effective treatment for pre-hepatic jaundice and neonatal physiological jaundice is phototherapy. Infusion of immunoglobulins is also used for treatment of pre-hepatic jaundice. Proper nutrition, steroids and immunosuppressant are used for treatment of hepatic jaundice. The treatment for post hepatic jaundice is decompression and surgery.

INTRODUCTION

Jaundice is defined as a yellowing of skin, mucous membranes and sclera due to the deposition of yellow- orange bile pigment i.e. bilirubin.[1] The bilirubin is an endogenously synthesized pigment that can be toxic specially in newborn children.[2]The bilirubin in unconjugated form has a typical spectrographical peak at 450 nm. [3]The word Jaundice is actually a derivative of French word 'Jaune' which means 'yellow'.[1] Jaundice indicates the hyper bilirubinemia and that excessive level of bilirubin may be in conjugated or unconjugated form. The clinical presentations of jaundice appear when bilirubin level exceeds 34.2 µmol/L or 2 mg/dL.[4] The substrate for the production of bilirubin is heme group. The heme is catabolized at alpha carbon bridge by an enzyme heme oxygenase and results in the liberation of iron, carbon monoxide and biliverdin. The biliverdin is further acted upon by biliverdin reductase to form bilirubin [5] 80 % of bilirubin is derived from the heme group of haemoglobin. This haemoglobin comes from the destruction of red blood cells in the reticuloendothelium of liver, spleen and bone marrow. The remaining 20% of bilirubin comes from multiple sources like myoglobin, cytochromes [6,7] 3.8 mg/kg or approximately 250-300 mg bilirubin is produced daily in normal adults. The amount of bilirubin production in neonates is much higher than adults.[8]The bilirubin produced is then transported to the liver in the bound form with plasma albumin. The dissociation constant for first albumin binding site is Kd=7 X 107M-1.9 Conjugation of bilirubin takes place in the liver by UDP-glucronyltransferase and this conjugation is essential for water solubility and elimination.[6,7]The activity of UDP-glucronyltransferase is influenced by age, gender, thyroid hormones and microsomal enzyme inducing agents, such as phenobarbital, rifampicin etc [9-13]· Conjugated bilirubin is excreted into the bile. The bile is then passed to the duodenum via biliary system. Inside the intestine some bilirubin is metabolized by the intestinal flora into urobilinogens and then reabsorbed. These urinobilinogens are then removed by the kidney and excreted via urinary system.[6,7].

Types of Jaundice

On the basis of causes Jaundice can be classified into three types.[4]

- Pre-hepatic Jaundice .
- Hepatic Jaundice .
- Post hepatic Jaundice .

1- Pre-hepatic Jaundice

Pre hepatic jaundice is such type of jaundice which is caused due to hemolysis therefore it is also known as hemolytic jaundice. The major cause of enhanced hemolysis is defective plasma membrane of red blood cells. This vulnerable cell membrane cannot bear the shear stress and hence ruptures resulting in hemolysis thus causing the increased serum bilirubin level.[14,15]

Etiology

The pre hepatic jaundice is mainly caused due to hemolysis. The causes of pre-hepatic/hemolytic jaundice are classified into two groups :

1- Congenital Causes

Congenital causes of hepatic jaundice involve following:[16,17]

Spherocytosis , Elliptocytosis , Congenital LCAT deficiency , Thalassemia, Sickle cell anemia , Stomatocytosis, Acanthocytosis, Echinocytes, GSH synthase deficiency, Pyruvate kinase deficiency, G6PD deficiency, Erythroblastosis fetalis.

2- Acquired causes

Acquired causes of pre-hepatic jaundice involve following: [16,17]
Resorption of extensive hematomas , Auto immune hemolysis, Transfusion reactions Trauma ,Microangiopathy, Hemolytic uremic syndrome, Long distance runners, Disseminated intravascular clot , Infections e.g. malaria ,Toxins e.g. snake venoms, Chemicals e.g. nitrites, aniline dyes, Paroxysmal nightly hemoglobinuria ,Thrombotic thrombocytopenic purpura ,Hypophosphatemia, Vitamin B12 deficiency,Folic acid deficiency,

Clinical presentations

Patients with hemolytic jaundice are presented with Anemia, Yellowing of sclera, dark yellow-brown colored urine, yellowish skin and high bilirubin levels.[18]

2- Hepatic jaundice :

Hepatic jaundice is a type of jaundice in which the basic defect lies within the liver mainly in the hepatocytes. The liver captures bilirubin from plasma proteins mainly albumin, then after conjugation excretes in the bile via biliary system. Any pathology of the liver leading to defect in capture, conjugation and excretion can cause hepatic jaundice. Main enzyme of conjugation is UDP- Glucronyltransferase. This is commonly immature at birth and its under-activity can cause so called Neonatal Physiological Jaundice. Further this enzyme can be defective due to the genetic mutation of the UTG1A gene on chromosome 2. This gene encodes for UDP- Glucronyltransferase and thus the defective conjugating enzyme leads to the hepatic jaundice.[19-21] Any defect in the hepatic excretory mechanism of bilirubin can also cause hepatic jaundice. The excretory mechanisms involve hepatocytic bile acid-independent secretion, hepatocytic bile acid-dependent secretion and bile ductular secretion. Any defect in the above mentioned excretory mechanisms can lead to the accumulation of bilirubin in blood causing hepatic jaundice.[22-31] .

Etiology

Hepatic jaundice is caused due to the defect in capture, conjugation and excretion of bilirubin by liver[32-35] .

Clinical presentations

The clinical presentations of hepatic jaundice include abdominal pain, fever, vomiting and nausea along with the complications involving satiety, gastrointestinal bleeding, diarrhea, anemia, edema, weight-loss and associated weakness, if unchecked leading to mental disturbances like kernicterus, coma or even death.[36,37]

3- Post hepatic jaundice :

Post hepatic jaundice is such type of a jaundice in which the cause lies in the biliary portion of hepatobiliary system. The major cause of post hepatic jaundice is extra-hepatic biliary obstruction. Therefore it is also known as obstructive jaundice.[38]

Etiology

The major cause of post hepatic jaundice is extra-hepatic biliary obstruction. [38]

Clinical presentation

The clinical manifestations of obstructive jaundice are dark urine, pale stools and generalized pruritus. History of fever biliary colic, weight loss, abdominal pain and abdominal mass are also the representatives of obstructive jaundice.[39] Obstructive Jaundice may lead to various complications including cholangitis, pancreatitis, renal and hepatic failure [40,41].

Differential diagnosis

The pre-hepatic jaundice can be differentiated from hepatic and post hepatic jaundice exclusively on the basis of elevated serum levels of unconjugated bilirubin and urobilinogen, which are raised in case of pre-hepatic jaundice. The serum levels on

conjugated bilirubin, alkaline phosphatase, Alanine transferase and Aspartate transferase are seen normal in the case of pre-hepatic jaundice. The urinary excretion of conjugated bilirubin is also not present in pre-hepatic jaundice.[42] The hepatic jaundice can be differentiated from post hepatic and pre hepatic jaundice on the basis of five times high bilirubin levels. In hepatic jaundice due to hepatitis the bilirubin levels may be ten times higher than their maximum values.[35,43] . Hepatic jaundice can be differentially diagnosed from post hepatic jaundice on the basis of abdominal ultrasonography and other radiological technique.[35] However the hepatic jaundice can be differentiated from pre-hepatic jaundice on the basis of diagnostic markers, like alpha-1 Antitrypsin, Ceruloplasmin,Immunoglobulins .[32,35,36,43]. Elevated serum bilirubin level along with the conjugation is a key diagnosis of post hepatic jaundice. Serum bilirubin is usually less than 20 mg/dL.

In pancreatic cancer the serum bilirubin may rise up to 40 mg/dL. Serum gamaglutamyl transpeptidase (Serum GGT), alkaline phosphatase and transaminases may be elevated. Tumour markers like CA-125, CA19-9 and CEA are usually elevated in cancerous obstruction.[39] The diagnosis of obstructive jaundice can further be confirmed by ultrasonography, plain abdominal x-ray, computed tomography, contrast-enhanced multi sliced computed tomography, endoscopic retrograde cholangiopancreatography (ERCP), Percutaneous trans- hepatic cholangiography (PTC), Endoscopic Ultrasound, Magnetic Resonance cholangiopancreatography (MRCP), Cholescintigraphy, Radionuclide scanning angiography and Staging Laparoscopy.[4,40,41].

Physiology/Biochemistry of Bilirubin production and transport .

Bile is a substance produced in the liver and contains bile salts, water, cholesterol, electrolytes, and bilirubin, which is a breakdown product of hemoglobin.

The formation of bilirubin from heme is essential for mammalian life, because it provides the body with the main means of elimination of heme. Eighty percent of the circulating bilirubin is derived from heme of hemoglobin from senescent red blood cells destroyed in the reticuloendothelium of the bone marrow, spleen, and liver [44]. Ten to twenty percent of the bilirubin comes from other sources such as myoglobin, cytochromes, and other heme- containing proteins processed in the liver. Initially, heme is oxidized at the alpha position to the green pigment biliverdin, which is then reduced at the gamma position to bilirubin. Bilirubin is virtually insoluble in aqueous solutions.

In blood it is reversibly but tightly bound to plasma albumin at a 1:1 ratio.[45].

Newly formed bilirubin is removed from the circulation very rapidly by the liver The processing of the serum bilirubin load by the hepatocytes occurs in four steps. These are: uptake, cytosolic binding, conjugation, and secretion. Hepatic uptake of bilirubin occurs with the dissociation of the albumin-bilirubin complex facilitated by plasma membrane proteins with subsequent translocation of bilirubin into the hepatocyte through a saturable protein carrier, which also binds other organic anions, but not bile salts.[46].

In the hepatocytes, bilirubin binds to two cytosolic proteins: ligandin and Z protein. The binding limits the reflux of bilirubin back to the plasma and delivers it to the endoplasmic reticulum for conjugation. Conjugation of bilirubin involves its esterification with glucuronic acid to form, first, a monoglucuronide, then a diglucuronide. The principal enzyme involved is uridine diphosphate (UDP)-glucuronyl transferase. Conjugation renders bilirubin water-soluble and is essential for its elimination from the body in bile and urine. Most of the conjugated bilirubin excreted into bile in humans is diglucuronide with a lesser amount of monoglucuronide [47]. Secretion of conjugated bilirubin from the hepatocyte to the bile canaliculi

involves a specific carrier and occurs against a concentration gradient. Conjugated bilirubin is excreted in bile, as a micellar complex with cholesterol, phospholipids, and bile salts, through the biliary and cystic ducts to enter the gallbladder, where it is stored; or it passes through Vater's ampulla to enter the duodenum. Inside the intestines, some bilirubin is excreted in the stool, while the rest is metabolized by the gut flora into urobilinogens and then reabsorbed. The majority of the urobilinogens are filtered from the blood by the kidney and excreted in the urine. A small percentage of the urobilinogens are reabsorbed in the intestines and re-excreted into the bile through the entero hepatic circulation[47,48].

Recent findings in the field of molecular biology and the human genome project have highlighted various proteins and genes responsible for the metabolism of bilirubin and some of these are being exploited in the treatment of cholestasis.[49-51].

Neonatal Hyperbilirubinemia

jaundice affects up to 84% of term newborns1 and is the most common cause of hos-pital readmission in the neona- tal period.[52]. Severe hyperbilirubinemia (total serum bilirubin [TSB] level of more than 20 mg per dL [342.1 μmol per L]) occurs in less than 2% of term infants and can lead to kernicterus (i.e., chronic bilirubin encephalopathy) and permanent neurode-velopmental delay.[53]. Therefore, it is impor-tant to systematically evaluate all infants for hyperbilirubinemia.

Acute bilirubin encephalopathy develops in one in 10,000 infants and presents with hypertonia, arching, retrocollis, opisthoto-nos, fever, and high-pitched cry.[52]. Data on progression of acute bilirubin encepha-lopathy to kernicterus are limited, but one study found that 95% of infants with acute bilirubin encephalopathy had full resolution of symptoms, and 5% had evidence of ker-nicterus by the time of discharge.[53]. Kernic-terus develops in one in 100,000 infants and manifests as athetoid cerebral palsy, audi-tory dysfunction, dental dysplasia, paraly-sis of upward gaze, and variable intellectual disability.

Risk factors for the development of severe hyperbilirubinemia include cephalhematoma or significant bruising, early gestational age, exclusive breastfeeding (especially unsuccessful breastfeeding and/ or weight loss of 8% to 10%), isoimmune or other hemolytic anemia, and a sibling with a history of neonatal jaundice.[54]. In addition to hyperbilirubinemia, earlier gestational age, hemolysis, sepsis, and low birth weight are associated with the development of bilirubin encephalopathy. One study found that less recommended range for phototherapy.[55]. However, screening decreases rates of read- mission for hyperbilirubinemia.[56].

How Should Infants with Jaundice Be Evaluated?

Visual inspection is not an accurate method to determine bilirubin levels and often misses severe hyperbilirubinemia.[57]. All infants who appear jaundiced should be evaluated with a risk score or TSB/TcB measurement. The bilirubin level should be interpreted accord- ing to the infants' age in hours. Further testing may be indicated depending on the infant's risk. Multiple studies have shown that TcB has a linear correlation with TSB at lower levels, but less so at higher levels.[54]. The American Academy of Pediatrics recommends the following laboratory tests for all infants with jaundice who require phototherapy: neonatal blood type, direct
antibody titer or Coombs test, complete blood count and smear, and direct/conjugated bilirubin level. However, a than 5% of healthy term infants with a TSB level greater than 30 mg per dL (513.1 µmol per L) developed acute bilirubin encephalopathy or kernicterus.[53].

What Are the Current Recommendations on Screening for hyperbilirubinemia?

The American Academy of Pediatrics recommends uni- versal screening with TSB or transcutaneous bilirubin (TcB) levels, or targeted screening based on risk factors[58]. Universal TSB/TcB screening can accurately identify infants whose TSB level is likely to exceed the 95th per- centile for age.[59,60]. Some studies have found that

the use of risk scores is as accurate as universal screening for pre- dicting hyperbilirubinemia.[61,62]. A combination of univer- sal screening and risk factor scoring seems to be the most effective method for identifying infants at risk of hyper- bilirubinemia[63,60].

Although screening can identify infants whose TSB level will likely exceed the 95th percentile, the U.S. Pre- ventive Services Task Force and the American Academy of Family Physicians found insufficient evidence that screening for hyperbilirubinemia is associated with improved clinical outcomes.[64,65]. Screening will iden- tify infants earlier who require phototherapy, but there is no evidence that phototherapy or exchange transfu- sion decreases the risk of bilirubin encephalopathy.[66].Universal screening increases phototherapy rates, pos- sibly inappropriately.

They also had elevated TSB levels after the initiation of phototherapy, whereas all infants with normal results had an appropri-ate decrease in TSB levels once phototherapy was started. These data suggest that addi-tional tests may be necessary only if jaundice occurs in the first 48 hours of life in an infant who meets the requirements for photother-apy, or if the infant is not responding appro-priately to phototherapy [66].

Treatment for Hyperbilirubinemia

1- PHOTOTHERAPY

Absorption of light through the skin converts unconjugated bilirubin into bilirubin photo-products that are excreted in the stool and urine , Infants who were deliv-ered at a younger gestational age or who are otherwise sick have lower thresholds for the initiation of phototherapy. The rate of decline of the TSB level after initiation of photother-apy is variable, but a 6% to 20% decrease is expected.[58]. In term infants without hemoly-sis, phototherapy can continue until the TSB level reaches 13 to 14 mg

per dL (222.4 to 239.5 µmol per L). Infants do not need to be kept in the hospital to check for rebound hyperbilirubinemia, which is rare.[67,68].

Although there is no standard protocol for phototherapy, principles include appro-priate light wavelength and irradiance, and maximization of exposed body surface area. Blue to green light with wavelengths of 460 to 490 nm is the most effective in converting unconjugated bilirubin. This is considered intensive phototherapy [69].

Infants should be naked except for their diapers to maximize the body surface area exposed to light. Types of phototherapy lights include conventional (halogen or fluorescent), light-emitting diode (LED), and fiber optic. LED and conventional lights are equally effective, with no difference in duration of phototherapy, rate of decline of the TSB level, or treatment failure.[69].

2- EXCHANGE TRANSFUSION

Although phototherapy is effective in the treatment of hyperbilirubinemia, exchange transfusion is occasionally indicated. A nomogram for exchange transfusion based on TSB levels is available.[58]. Exchange trans-fusion should be performed in infants with TSB levels in the range indicated by the jaundice (number needed to harm = 4) [70]. Infants whose breastfeeding was interrupted for treatment of jaundice were more likely to not be breastfed at one month of age (number needed to harm = 4). Another study found that maternal interaction with health care profession-als (e.g., breastfeeding orders, encouragement) was the strongest predictor of breastfeeding continuation for infants with jaundice [71].

3- Breastfeeding :

Breastfed infants are three times more likely to have a TSB level greater than 12 mg per dL (205.3 µmol per L) and six times more likely to have a level greater than 15 mg per dL (256.6 µmol per L).[72]. The exact mechanism for breastfeeding-related jaundice is

unknown, but may involve decreased caloric intake, inhibition of hepatic bilirubin excretion, and increased intestinal bilirubin resorption .

One study compared neonates who were exclusively breastfed with those who received supplemen-tal formula if they had significant weight loss, and others who were formula fed.[73]. The results suggest that caloric deprivation—not necessarily breastfeeding-increases the risk of hyperbilirubinemia. Increasing the frequency of breastfeeding decreases the likelihood of significant hyperbilirubinemia.5 Signs of adequate intake in breast-fed infants include four to six thoroughly wet diapers per day, three to four stools per day by the fourth day of life, and a transition to seedy, mustard-colored stools by the third or fourth day of life.[58].

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