

Acetaminophen use in patients with Gilbert's syndrome

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Dedication

Most importantly I would like to thank God for blessing me with opportunity to be where I am at today. In addition, thanks must be given to my friends and family. Especially my parents, Jack and Jane, and my girlfriend Jana for all their love and support which has enabled me to accomplish all that I have.

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A 14-year-old boy with acute jaundice

A 14-year-old boy from Nepal presented with history of scleral icterus for 10 days. The boy had no other complaints. The child had a previous history of a similar illness twice before: the first approximately year prior and the second 3 months before this recurrence. No medical intervention was previously sought because the scleral icterus resolved on its own. This time the scleral icterus quickly returned, and the child presented again to the pediatric ward for the third time. Upon physical exam, the only abnormal finding present was mild jaundice. Urine and stool were normal, and chest film showed no abnormalities. Lab findings included normal hemoglobin, differential count, ESR and platelets. Reticulocyte count and LFTs were also found to be normal. No features of hemolysis were discovered on a peripheral blood smear. Hepatitis B and C testing found an absence of HBsAg and AntiHCV, no other hepatitis testing was performed. The only significant finding was elevated unconjugated hyperbilirubinemia (Manandhar, Gurubacharya, Baral, & Manandhar, 2003).

Hyperbilirubinemia is not uncommon. For example, sixty-five percent of newborns develop clinical jaundice with a total bilirubin level above 5 mg/dL (normal 0.1- 4.9mg/dL) during the first week of life (Thilo & Rosenberg, 2004). The differential diagnosis of hyperbilirubinemia is extensive. A thorough history and physical exam must be performed. The use of other labs such as LFT, CBC, and UA can help guide the clinician and help generate a reasonable differential diagnosis. The differential diagnosis may be further stratified as primarily conjugated hyperbilirubinemia versus non-conjugated hyperbilirubinemia (Wolkoff, 2005).

The first main group of hyperbilirubinemias into which to divide the differential diagnoses is the conjugated hyperbilirubinemias. Causes of conjugated hyperbilirubinemia fall into three categories. The first mechanism that can be a common cause of conjugated hyperbilirubinemia is obstruction. An intra-hepatic or extra-hepatic obstruction can cause an elevation in serum conjugated bilirubin. Such causes can be from gall stones, cholestasis, primary/metastatic cancers, and hematomas. In fact, obstruction in the biliary tree is the most common cause of conjugated hyperbilirubinemia (Murray, 2006). Another common reason to find elevated serum conjugated hyperbilirubinemia levels is from liver disease, such as hepatitis and cirrhosis of the liver. Serum testing and liver biopsy may be indicated when hepatitis and/or liver cirrhosis are suspected. Certain familial defects are another cause of conjugated hyperbilirubinemia. Although rare, they should not be overlooked when other more common etiologies have been ruled out. Dubin-Johnson syndrome, rotor syndrome, benign recurrent intrahepatic cholestasis, and progressive familial intrahepatic cholestasis are four rare but documented familial causes of conjugated hyperbilirubinemia (Wolkoff, 2005).

The second main group of differential diagnoses are hyperbilirubinemias that are unconjugated in nature. Unconjugated hyperbilirubinemia usually occurs due to an increase in serum bilirubin, which causes the conjugation pathway to become overwhelmed, due to massive hemolysis, an acquired conjugation defect, or a familial disease causing a diminished or absent conjugation system (Barrett, 2006). Massive hemolysis can rapidly cause the bilirubin-UGT pathway to become overwhelmed, causing an increase in unconjugated serum bilirubin. A classic example of

hyperbilirubinemia occurring through hemolysis is the massive RBC destruction that may occur when a child is born to a mother with an Rh incompatibility (Barrett). A common cause of acquired conjugation defect is advanced hepatitis or cirrhosis of the liver. However, this mechanism is commonly overlooked because there is only a small reduction in bilirubin-conjugating capacity (Wolkoff, 2005).

Finally, the last main mechanism of unconjugated hyperbilirubinemia is a diminished or absent conjugation system. The three main disorders causing a diminished or absent conjugation system are Crigler-Najjar Syndrome type I, Crigler-Najjar Syndrome Type II and Gilbert's syndrome. These three familial disorders characterized by differing degrees of unconjugated hyperbilirubinemia have long been recognized (Wolkoff, 2005). Crigler-Najjar Type I is the most severe and is characterized by extremely high levels of unconjugated hyperbilirubinemia that can reach levels of 20 to 45 mg/dL. It is observed at birth and continues for life. In hepatic tissue, there is no detectable expression of UGT1A1, an enzymatic system used to conjugate bilirubin. Phenobarbital or other enzyme inducers do not cause UGT1A1 activity or decrease serum bilirubin levels. Before phototherapy was available, most patients with Crigler-Najjar Type I died of bilirubin encephalopathy in infancy or early childhood (Wolkoff). Crigler-Najjar Type II, differs from Type I in many ways. The average bilirubin concentrations are lower in Crigler-Najjar Type II, and it is infrequently associated with bilirubin encephalopathy when compared to type I. UGT1A1 in the liver is usually present at reduced levels in Type II, whereas UGT1A1 is absent in Crigler-Najjar Type I. With Crigler-Najjar Type II, a reduction in serum bilirubin concentrations can be seen with the use of Phenobarbital and other enzyme inducers (Wolkoff).

Gilbert's syndrome is the final familial cause of unconjugated hyperbilirubinemia in humans. Gilbert's syndrome is an autosomal recessive condition and the most common form of inherited cause of unconjugated hyperbilirubinemia (Manandhar et al., 2003).

Gilbert's syndrome occurs in approximately 7% of the population and is characterized by intermittent jaundice in the absence of hemolysis or underlying liver disease. The hyperbilirubinemia is usually mild and by definition less than 6 mg/dL, however, most patients exhibit levels of less than 3 mg/dL. Bilirubin levels fluctuate often and may even decline to normal ranges as much as one third of the time (Mukherjee, 2006). The hyperbilirubinemia caused by Gilbert's syndrome is due to the deficiency of the bilirubin-UGT enzyme, which results in an insufficient amount of bilirubin conjugation taking place in the liver. This is the mechanism responsible for the unconjugated hyperbilirubinemia in Gilbert's syndrome (Monaghan, Ryan, Seddon, Hume, & Burchell, 1996). Although the disease is asymptomatic in a majority of the patients, symptomatic patients with Gilbert's syndrome may experience abdominal cramping, fatigue, and general malaise. Gilbert's syndrome may also present with scleral icterus and mild jaundice, both precipitated by hyperbilirubinemia.

The History of Gilbert's Syndrome

In 1901, a French gastroenterologist named Augustine Gilbert and his partner Pierre Lereboullet were the first to describe Gilbert syndrome. In Germany, the medical literature refers to Gilbert's syndrome as "Morbus Meulengracht" named after Meulengracht who described such a syndrome in 1939. Later, in 1962, Arias documented a disorder in which eight patients had chronic non-hemolytic jaundice. A paper published by Sleisenger and colleagues (1967), studying four generations of an Irish family, noted that the unconjugated hyperbilirubinemia resulted from a deficiency in hepatic glucuronyl transferase. The paper did not note any significance in the family's Irish heritage as a specific predisposing factor to Gilbert's syndrome. This particular family was only used to demonstrate the pattern of genetic transmission.

Clinical Presentation

Many patients with Gilbert's syndrome are entirely asymptomatic. The disease is commonly an incidental finding unrelated to the chief complaint. A paper published by Gitlin (1977) reported symptomatic findings of patients with diagnosed Gilbert's syndrome. The most common findings were vague symptoms that included recurrent asymptomatic jaundice in 74% and feelings of malaise in 66% of the patients. Asthenia was also found in 65% of the subjects, and 52% of patients complained of vague abdominal. Although the research performed by Gitlin involved only 26 patients, other research has demonstrated jaundice to be the most common symptom (Radu & Atsmon, 2001; Sleisenger et al. 1967). Usually a bilirubin level of at least 3 mg/dL is

necessary for jaundice to be present (Friedman, 2007). Certain factors are known to exacerbate the hyperbilirubinemia associated with Gilbert's syndrome. Dehydration, fasting, acute illness, menstrual periods, and stress from trauma or overexertion are common causes of exacerbation of hyperbilirubinemia among Gilbert's syndrome patients.

Bilirubin Physiology

In adults, baseline serum bilirubin levels are higher in men (0.7 mg/dL) than in women (0.5 mg/dL) and are lower in non-Hispanic blacks compared with non-Hispanic whites and Mexican Americans (Zucker, Horn, & Sherman, 2004). Bilirubin is the primary waste product of heme metabolism. In adults, 250-350 mg of bilirubin is produced daily. Approximately 70-80% of daily bilirubin is derived from hemoglobin (Pratt & Marshall, 2005) with other bilirubin from heme proteins such as myoglobin, cytochromes, catalase, and the destruction of erythroid cells (Smith, Chemmanur, & Donnelson, 2006). The natural structure of bilirubin causes it to be extremely hydrophobic and lipophilic, which is why unconjugated bilirubin must be transported in the plasma bound to albumin. When albumin-bound bilirubin reaches the liver, the unconjugated bilirubin detaches from albumin and is transported through the hepatocyte membrane by facilitated diffusion. Within the hepatocyte, bilirubin can bind with two different intracellular proteins, cytosolic Y protein (ligandin or glutathione S-transferase B) and cytosolic Z protein (fatty acid-binding protein [FABP]) (Pratt & Marshall; Smith et al.). The binding of bilirubin to these proteins decreases the likelihood of bilirubin getting

back into the plasma. In order for bilirubin to be eliminated from the body, it has to be excreted into bile. This is a problem due to bilirubin's hydrophobic structure. To make bilirubin more hydrophilic, glucuronic acid is enzymatically attached via esterification. This esterification is catalyzed by bilirubin uridine-diphosphate glucuronosyltransferase (bilirubin-UGT), which is located in the endoplasmic reticulum of the hepatocytes (Barrett, 2006). This reaction leads to the production of water-soluble bilirubin. This conjugation reaction is the critical process for bilirubin to be excreted into bile.

Pathophysiology of Gilbert's Syndrome

The hyperbilirubinemia in Gilbert's syndrome can be attributed to the decrease in activity of bilirubin-uridine diphosphate glucuronyl transferase (bilirubin-UGT). The main purpose of the Bilirubin-UGT is to conjugate bilirubin with a polar group. This polar group causes bilirubin to become more water soluble. This increase in solubility, allows for bilirubin to be excreted through bile. This enzymatic system is located primarily in the endoplasmic reticulum of hepatocytes (Barrett, 2006). Bilirubin-UGT is encoded by a single gene, UGT1. UGT1 is located on chromosome 2 at locus 2q.37 (Moghrabi, Clarke, Boxer, & Burchell, 1993). There are several isoforms of the enzyme gene. Research conducted by Bosma in 2003 found that individuals with Gilbert's syndrome had a normal coding region of the UGT1A1 gene, but were homozygous for two extra bases (TA) in the TATAA¹ box of the 5 promoter region of the. The longer TATAA box causes a reduction in the expression of the gene. The frequency of the abnormal allele

¹ A TATA box is a DNA sequence in the promoter region of most genes. It is involved in the process of transcription by RNA polymerase.

was 40% among studied subjects. People who were homozygous for the longer TATAA element had significantly higher serum bilirubin levels than the other normal subjects (Bosma; Radu & Atsmon, 2001).

Diagnosis of Gilbert's Syndrome

The diagnosis of this syndrome is largely based on clinical judgment. Of three commonly used diagnostic tests, however, elevation of bilirubin levels during fasting is used as the most common diagnostic tool for Gilbert's syndrome (Radu & Atsmon, 2001). In patients with Gilbert's syndrome, a rise in bilirubin can be as significant as 2- or 3-fold increase during fasting. Although a sensitive test, fasting is not highly specific; the same increase in bilirubin can be present if the patient has liver disease or hemolysis. A paper published in 2003 by Manandhar and colleagues, stated, in the absence of other disease processes, Gilbert's syndrome may be suspected with the presence of unconjugated hyperbilirubinemia under certain conditions. The conditions are not only normal liver function tests and liver enzymes, but also a normal CBC, reticulocyte count and blood smear. Other, less popular tests can be used in confirming the diagnosis of Gilbert's syndrome. Nicotinic acid (niacin) has been used to help diagnose Gilbert's syndrome. While normally used as a cholesterol-lowering agent, 50 mg of nicotinic acid via IV will cause a 2- to 3-fold increase in unconjugated bilirubin within 3 hours. Although sensitive, this test is non-specific and may be positive in unconjugated hyperbilirubinemia regardless of the cause and, therefore, is probably of no value in differentiating Gilbert's syndrome from other entities, such as chronic liver

diseases (Dickey, McAleer, & Callender, 1991). Another diagnostic assessment uses enzymatic inducers such as phenobarbital. Normally phenobarbital is a barbiturate used as an anti-convulsant. In this case, it is used to induce the hepatic conjugation system, which, in return, will lower the plasma bilirubin levels in patients with Crigler-Najjar Type II as well as Gilbert's syndrome. Other methods of diagnosing Gilbert's syndrome, such as thin-layer chromatography and polymerase chain reaction test are rarely used outside of a research setting.

Gilbert's Syndrome and Acetaminophen

In the United States, acetaminophen is the number one used analgesic (Larson et al., 2005), and in January 2004, the FDA released a statement stating that acetaminophen is a constituent in over 600 over-the-counter and prescription medications. A research paper by Larson and his colleagues in 2005 noted the incidence of acute liver failure (ALF) due to acetaminophen toxicity rose from 28% in 1998 to 51% in 2003. This now makes acetaminophen toxicity the most frequent cause of acute liver failure in the United States. For the 70-kg adult male, a dosage of >4 gm per day could cause an overdose. The dosage needed to cause an overdose could potentially be lower for Gilbert's syndrome patients. Research does not suggest an increased risk of hepatotoxicity with appropriate therapeutic usage of acetaminophen (adult dosing 325-1000 mg PO/PR q 4-6 h. Max 1g/dose, 4g/24 hours) (Ullrich et al., 1987). About 60% of acetaminophen is eliminated via glucuronidation (Prescott & Critchley, 1983), and there is potential for higher than normal plasma levels of acetaminophen among Gilbert's syndrome patients because of their deficiency in

glucuronidation. Gunn rats have been repeatedly used to demonstrate this potential toxicity. Gunn rats have deficient UGT enzymatic activity just as Gilbert's syndrome patients do. A difference between Gunn rats and humans is variation between their respective isoenzyme deficiency. This difference causes more severe toxicity at smaller doses of acetaminophen in the Gunn rat.

Esteban and Perez-Mateo (1999) performed a study on Gilbert's syndrome patients and paracetamol (paracetamol is the International Nonproprietary Name, where as acetaminophen is the United States adopted name). Their 32 patients were given 1.5 g of paracetamol orally. They found one of their subgroups experienced a marked decrease in glucuronidation ($P = 0.0012$) and an increase in oxidation ($P = 0.0051$). This is important because any decrease in acetaminophen/paracetamol metabolism via normal pathways correlates with an increase in metabolism via a toxic route. Esteban and Perez-Mateo believe these changes could mean that people in this subgroup could be more prone to liver damage when using supra-therapeutic doses of paracetamol. A similar study was performed in 1992 by de Morais, Uetrecht, and Wells. The researchers gave 12 patients with Gilbert's Syndrome a supra-therapeutic 20 mg/kg acetaminophen IV. Acetaminophen was given over a 12-minute period as a 12.5 mg/mL solution into a superficial forearm vein. Formation of the acetaminophen glucuronide conjugate, measured by high-performance liquid chromatography, was quantified by the ratio of the area under the plasma concentration-time curve (AUC) from 0 to 2 hours for the acetaminophen glucuronide divided by the AUC for acetaminophen. Acetaminophen bioactivation was quantified by the molar percentage of acetaminophen excreted in the urine as glutathione-derived conjugates (cysteine and mercapturic acid) over a 24-hour

period. They found glucuronidation was decreased, indicating acetaminophen metabolism via the major pathway of elimination was reduced. This allowed for more of the acetaminophen to be shunted through the toxifying route. This article does not suggest patients with Gilbert's syndrome are at an increased risk using therapeutic doses of acetaminophen. However, more research needs to be looked at with Gilbert's syndrome patients using supra-therapeutic doses of acetaminophen. Potential studies need more subjects and research more common routes of acetaminophen ingestion (PO). Until such studies are available, clinicians should keep a close watch on acetaminophen use their patients with Gilbert's syndrome.

To further complicate matters, alcohol consumption may also interfere with acetaminophen metabolism. There are conflicting thoughts about the amount of alcohol and acetaminophen needed to precipitate toxicity in the general population. It is believed by some researchers that even "moderate social drinkers" (not defined by author) are at risk for toxicity when using acetaminophen (Draganov, Durrence, Cox, & Reuben, 2000). Other researchers believe that ethanol is not capable of causing increased toxicity when combined with therapeutic doses of acetaminophen (Rumack, 2004). With acetaminophen being a constituent in over 600 over-the-counter and prescription medications, it is not out of the realm of possibility that patients could be using more acetaminophen than they know. In addition, if these patients are consuming alcohol one must worry about a possible cumulative affect endangering the patient. Until a more research based opinion is available, clinicians must educate Gilbert's syndrome patients of the potential hazards of using acetaminophen and alcohol separately or together.

Management/Treatment of Gilbert's Syndrome

Under most normal circumstances, there is no required treatment for Gilbert's syndrome. The most important management strategy is patient education and reassurance. Patients with Gilbert's syndrome need to be educated about possible complications. These may include exacerbations of jaundice, especially when the patient is using acetaminophen and/or alcohol. Wolkoff (2005) states that most xenobiotics² metabolized by glucuronidation appear to be normal in Gilbert's syndrome. However, Harrison's goes on to say that it has been reported that there may be abnormal metabolism of menthol, estradiol benzoate, acetaminophen, tolbutamide, and rifamycin. If the jaundice becomes severe and/or the appearance is bothering the patient, a reduction in the serum bilirubin can be temporarily achieved with Phenobarbital injections. Caution should be used due to the habit forming nature of Phenobarbital. Overall, the prognosis associated with Gilbert's syndrome is excellent. The syndrome typically has no association with deleterious complications and those who have it can lead normal lifestyles (Manandhar et al., 2003).

Benefits of Gilbert's Syndrome?

Over the past few years, researchers have looked at the potential cardioprotective effects of increased bilirubin levels (Stocker, Glazer, & Ames, 1987; Vitek et al., 2001; Sedlak & Snyder 2004). As a known potent antioxidant, studies have

² Foreign to the body or to living organisms. Used of chemical compounds

shown higher bilirubin levels are associated with a decreased risk of myocardial infarction and other cardiovascular disease events (Sedlak & Snyder). In 2003, Novotny and Vitek performed a meta-analysis of 11 studies on the epidemiology of atherosclerotic diseases and how they relate to serum bilirubin levels. They used three separate types of analyses to compare the results. Nonparametrical, regression and stratified testing all demonstrated an inverse dose response relationship between the atherosclerosis and serum bilirubin levels. To strengthen this point further, a different study by Vitek et al. (2000) looked at the prevalence of ischemic heart disease between patients with diagnosed Gilbert's syndrome and the general population. Ischemic heart disease has a prevalence of 2% in patients with Gilbert's syndrome, compared to 12.1% of the general population. This study indicated elevated bilirubin levels may have more of a cardioprotective role than HDL levels when related to ischemic heart disease. Research has consistently shown the extraordinary antioxidant properties and benefits of bilirubin in the pathological setting.

Another potential benefit of chronic hyperbilirubinemia may exist. The relationship between serum bilirubin levels and incidence of colorectal cancer has been a topic of debate. Researchers such as Zucker and his colleagues believe there is an inverse relationship between serum bilirubin concentrations and colorectal cancer (2004). The hypothesis stems from the ability of unconjugated bilirubin to traverse cellular membranes, which eases entry into existing tumor cells. This allows the unconjugated bilirubin to stimulate apoptosis in colon cancer cells (*in vitro*). Also, in normal cells cycling of certain molecules (biliverdin reductase-catalyzed redox) with unconjugated bilirubin is believed to be an important protective mechanism against

cellular oxidative injury (Zucker, Horn, & Sherman 2004). There are, however, researchers such as Ionnou, Liou, and Weiss who strongly disagree. A paper published by Ionnou and his colleagues (2006) looked at a population-based cohort study of serum bilirubin levels and colorectal cancer. Even after adjusted analyses, the data stated in their study did not demonstrate any association between elevated serum bilirubin levels and a decreased incidence of colorectal cancer. Researchers in this area feel more needs to be done to look at these potential chemopreventive properties of bilirubin.

Conclusion

In conclusion, Gilbert's syndrome is a genetic cause of chronic unconjugated hyperbilirubinemia. Benign in nature, under normal circumstances patients with Gilbert's syndrome can expect to live a normal life. Recent studies show there may even be protective effects of the chronic hyperbilirubinemia associated with Gilbert's Syndrome. As health care providers, diagnosed patients should be educated about their condition and reassurance about the generally benign syndrome should be given. However, warning should be given about the most commonly used analgesic, acetaminophen. Although no articles in the literature suggest hepatotoxicity with recommended dosing, certain studies have shown a potential for people with Gilbert's syndrome to be more prone to complications with supra-therapeutic doses of acetaminophen. In addition, some researchers believe alcohol has a deleterious effect on proper acetaminophen processing causing a potential for hepatotoxicity when used concurrently. Therefore,

patients with Gilbert's syndrome taking supra-therapeutic doses of acetaminophen and drinking alcohol may be at an even greater risk of hepatotoxicity when compared to the person without Gilbert's syndrome. Until more evidence is available, health care providers should take time to explain these potentials to patients with Gilbert's syndrome.

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Abstract

Objective. The relationship between patients with Gilbert's syndrome and acetaminophen use is still unclear. **Method.** MEDLINE, PUBMED, OHIOLINK, and Google Scholar were searched for Gilbert's syndrome and acetaminophen use. **Results.** Patients with Gilbert's syndrome taking therapeutic levels of acetaminophen are not in danger of hepatotoxicity. **Conclusions.** (1) Patients with Gilbert's syndrome can expect to live a normal life; (2) there may even be protective effects of the chronic hyperbilirubinemia associated with Gilbert's Syndrome; (3) no articles in the literature suggest hepatotoxicity with recommended dosing, certain studies have shown a potential for people with Gilbert's syndrome to be more prone to complications with supra-therapeutic doses of acetaminophen; and (4) alcohol may have a deleterious effect on acetaminophen processing causing a potential for hepatotoxicity when used concurrently. Patients with Gilbert's syndrome taking supra-therapeutic doses of acetaminophen and drinking alcohol may be at a greater risk of hepatotoxicity.