

## CASE REPORT

### ANAESTHETIC MANAGEMENT OF PATIENT WITH GILBERT'S SYNDROME

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**ABSTRACT:** Gilbert's syndrome is characterized by mild unconjugated hyperbilirubinemia without either structural liver disease or hemolytic anemia. Bilirubin is produced during the breakdown of hemoglobin and hemoproteins. Since bilirubin is insoluble in water, it must be converted into a soluble conjugate form in the liver before elimination from the body. In the liver, enzyme uridine diphosphate (UDP) glucuronosyltransferase converts the bilirubin into the mixture of monoglucuronides and diglucuronides referred as conjugated bilirubin. The relative deficiency of UDP glucuronosyltransferase results in reduced activity nearly 10-30% normal, leading to unconjugated hyperbilirubinemia, Gilbert's Syndrome (GS). Since majority of anesthetic agents require this enzyme for their metabolism and excretion, its deficiency leads to potential accumulation of such drugs resulting in anesthetic toxicity with adverse outcome. Anesthetic management of Patient with Gilbert's Syndrome is quite challenging. A thorough knowledge of pathophysiology and precipitating factors of GS are essential for safe administration of anesthesia.

**KEYWORDS:** Gilbert's syndrome, Hyperbilirubinemia, Glucuronosyltransferase, Anesthesia.

**INTRODUCTION:** Gilbert's Syndrome (GS) is characterized by mild unconjugated hyperbilirubinemia without either the structural liver disease or hemolytic anemia. Frequency of GS ranges from 2 to 13%<sup>[1]</sup> and relative deficiency of Uridine Glucuronosyl Transferase (UGT) leads to poor uptake of unconjugated bilirubin by hepatocytes.<sup>[2]</sup> GS is associated with defect in both bilirubin uptake and conjugation. Majority of anesthetic agents require enzyme UGT for their metabolism and excretion, its deficiency results in potential accumulation of drugs leading to catastrophic outcome. Hence, anesthetic management of Patient with GS is quite challenging.

In GS serum bilirubin concentration is most often <3mg/dl, although both higher and lower values are common. More elevated values are associated with stress, fatigue, starvation, alcohol use and intercurrent illness,<sup>[3]</sup> Anesthetic management involves proper preoperative evaluation, minimizing fasting, glucose infusion in the early morning prior to the surgery, adequate post-operative analgesia, avoidance of drugs that are metabolized by glucuronosyltransferase in the liver<sup>[4]</sup> and surgery scheduled as first case on priority basis.

**CASE REPORT:** A 25 years old male, weighing 55kg was posted for elective FESS (ENT surgery) under general anesthesia. He was a known case of congenital hyperbilirubinemia, Gilbert's syndrome since 2 years. His persistent yellowish discoloration of sclera used to get aggravated during stress and infection, subsequently resolving on its own without any medical intervention. He was quite anxious and worried about the complications of surgery and anesthesia.

On preanesthetic evaluation patient's pulse rate was 72bpm, blood pressure 120/80mmHg with icterus. RS, CVS, and abdominal examination did not reveal any abnormality. Laboratory investigations revealed hemoglobin level 10.8g%, platelet count 1.5L/cumm, total bilirubin 5.2 mg/dl, ALT 46IU, AST42IU/L, urine was negative for urobilinogen, bilepigments and bilesalts.

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Peripheral smear showed normochromic RBCs with moderate anisocytosis and spherocytosis. ECG showed no abnormalities. Patient and his relatives were explained about the risk of post-operative hyperbilirubinemia, possibility of hepatic dysfunction and informed consent was obtained.

Pre anesthetic approach was 8 hours fasting with surgery scheduled for first morning period. He was premedicated with Alprozolam 0.5mg and Ranitidine 150mg orally on the night before and early morning of surgery with sips of water. 5% Dextrose drip was started at 6am in the morning of the surgery, and converted to NS drip in the operation theater at the start of surgery. Monitoring in the operating theater consisted of pulseoximetry, non-invasive blood pressure, cardioscopy and capnography commenced after tracheal intubation. Anesthesia induced with IV Fentanyl 100mcg, Propofol 100mg Atracurium 25mg. Trachea intubated with cuffed ETT 8mm internal diameter. Anesthesia maintained with Isoflurane, Nitrous oxide, Oxygen with circle absorber in the system with intermittent positive pressure ventilation throughout the course of operation. Half the bolus dose of Atracurium repeated after 30 minutes of initial dose, no further dose required until the completion of surgery. The surgery lasted for one hour; neuromuscular blockade reversed with 2.5 mg of Neostigmine and Glycopyrrolate 0.5mg. Post extubation, the patient was hemodynamically stable. Intravenous Nalbuphine 10 mg was administered after tracheal extubation for post-operative analgesia. Postoperatively, the patient was transferred to surgical intensive care unit for further management. Hydration was optimized with NS and 5% Dextrose. Patient was allowed oral supplementation six hours after extubation. His Serum bilirubin and LFT followed up daily for two days and was discharged on third day without complications, with instructions of reporting immediately to the ENT OPD or emergency department of the hospital for symptoms like dizziness, malaise or abdominal pain or recurrence of jaundice.

**DISCUSSION:** Augustine Gilbert and Pierre Lereboullet first described the Gilbert's Syndrome the most common unconjugated hyperbilirubinemia in 1901.<sup>[5]</sup> GS is a rare form of unconjugated hyperbilirubinemia in the absence of structural liver disease or hemolytic anemia; having male predominance in the ratios male: female ranging from 1.5:1 to >7:1. Older studies of GS were consistent with autosomal dominant inheritance with variable expressivity. However, studies of UGT1 gene in GS have indicated variety of molecular genetics bases for the phenotypic picture and several patterns of inheritance. Reduced activity of the conjugating enzyme, bilirubin Uridine Diphosphate Glucuronosyl Transferase (UGT) results in mild unconjugated hyperbilirubinemia. Bilirubin-UGT is one of the several UGT enzyme isoforms responsible for conjugation of wide range of substances; including anesthetic drugs, hormones and neurotransmitters.<sup>[6]</sup> Majority of patients with GS are asymptomatic however, may be associated with 70% reduction of glucuronidation activity in the liver.

A thorough knowledge of pathophysiology and precipitating factors of GS is essential for safe administration of anesthesia. Surgery and anesthesia are stressful events, may lead to increase in bilirubin postoperatively.<sup>[7]</sup> Many anesthetic drugs are metabolized or bio transformed by various enzymes including glucuronosyl transferase in the liver. GS may lead to accumulation of such drugs resulting in adverse outcome. The relative deficiency of glucuronosyl transferase leads to increase in the level of unconjugated bilirubin in the blood and clinical jaundice is seen with the bilirubin level of >3mg/dl. Surgery, infection, fatigue, exercise, prolonged alcohol intake and menstruation can aggravate the symptoms of GS. Hence, perioperative priorities involve minimizing fasting, glucose infusion in the early morning and early surgery preferably the first case.

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In our case 5% Dextrose started early in the morning of the surgery to avoid dehydration and hypoglycemia. IV supplementation converted to normal saline intraoperatively to take care of glycemia and avoiding hyperglycemia, due to increased secretion of counter regulatory hormones like catecholamine, cortisol, glucagon and growth hormone.<sup>[8]</sup> Fentanyl considered safe as its effect after single bolus dose is terminated by redistribution to muscle and fat; subsequent metabolism is primarily by N-dealkylation and dehydroxylation<sup>[9]</sup> but not by conjugation. Remifentanyl is safer alternative due to its ultra-short duration of action and ester degradation by plasma and tissue esterases. Propofol was chosen over Thiopentone or Ketamine as it has higher clearance than liver blood flow suggesting extra liver excretion pathway, further Thiopentone and Ketamine alter the liver function in dose dependent manner.<sup>[10, 11]</sup> Atracurium was preferred due to its alternate metabolic pathways; Hoffmann degradation and ester hydrolysis. Mivacurium and Cis -atracurium are other safer alternatives due to their similar metabolic pathways.<sup>[12]</sup>

Isoflurane was considered safer; since only 0.2% of drug is metabolized by liver,<sup>[13]</sup> it also preserves liver blood flow. Good post-operative analgesia was attained with intravenous Nalbuphine. Paracetamol and Morphine specifically avoided. Even though paracetamol is not metabolized by glucoronyl transferase it is metabolized by another enzyme which is also deficient in GS, making them susceptible to the potential risk of paracetamol toxicity.<sup>[14,15]</sup> Morphine is metabolized by conjugation in the liver so it exerts prolonged effect in patients with GS.<sup>[16]</sup> Definitely, regional anesthesia techniques such as spinal anesthesia, epidural anesthesia/ analgesia<sup>[17]</sup> and peripheral nerve blocks are useful techniques whenever possible. These techniques provide rapid and complete anesthesia, limit adverse events providing prolonged optimal post-operative pain relief. But for this patient general anesthesia was indicated hence, with proper planning, preparation and using safe drugs anesthesia was conducted successfully.

**CONCLUSION:** To conclude, GS poses several challenges to anesthesiologists, relative deficiency of glucoronyl transferase leads to anesthetic toxicity and catastrophic outcome. Regional anesthetic techniques should be preferred over general anesthesia whenever possible however, if general anesthesia is required, one should prefer anesthetic agents with extra hepatic pathway for metabolism and excretion.

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