Case Report

General anesthesia in a patient with Gilbert's syndrome

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Abstract

Gilbert's syndrome, caused by relative deficiency of glucuronyl transferase is the commonest cause of congenital hyperbilirubinemia. We report anesthetic management in a case of Gilbert's syndrome for laparoscopic cholecystectomy under general anesthesia. Avoiding drugs which use this enzyme for its metabolisim or excretion, and minimizing the stress during the perioperative period allows safe conduct of anesthesia for these patients.

Key words: Anesthesia, bilirubin, Gilbert's syndrome, jaundice

Introduction

Gilbert's syndrome (GS) is an inherited disorder of hepatic bilirubin metabolism occurring in the population with a frequency ranging from 2 to 13%.[1,2] The condition is caused by relative deficiency of glucuronyl transferase and poor uptake of unconjugated bilirubin by hepatocytes.[3] Many anesthetic drugs metabolized in the liver through this pathway can potentially accumulate leading to adverse outcomes. Despite the significant incidence, reports on anesthetic management of patients with Gilbert's syndrome are few.

Case Report

A 35-year-old male weighing 65 kg was posted for elective laparoscopic cholecystectomy. He was diagnosed with Gilbert's syndrome 5 years ago on investigation for persistent yellowish discolouration of sclera which got aggravated during periods of stress and illness and resolved subsequently without any medical intervention. He was quite anxious that his condition would worsen on surgery. His liver function status, on preoperative evaluation 2 days before surgery, revealed aspartate aminotransferase (AST) and alanine transaminase (ALT) of 38 and 42 IU/L, respectively, while bilirubin was 5.6 mg/dl. Although a familial increase of alkaline phosphatase has been described in Gilbert's syndrome, being a diagnosed case, it was not repeated preoperatively. He was premedicated with alprazolam 0.5 mg and ranitidine 150 mg orally on the night before and on morning of surgery with sips of water. He was scheduled first on the list at 7:30 am. A 5% dextrose drip was started at 5 am on the morning of surgery and in the theatre and it was converted to a normal saline drip at the start of surgery. After intravenous (IV) ondansetron 4 mg, anesthesia was induced with IV fentanyl 100 μg, propofol 130 mg and 30 mg of atracurium. Trachea was intubated with cuffed endotracheal tube of 8.0 mm internal diameter. Anesthesia was maintained with isoflurane, nitrous oxide and oxygen by the circle system. The intraoperative period was uneventful with stable hemodynamics. General anesthesia was maintained with isoflurane, nitrous oxide and oxygen through the circle system and intermittent positive pressure ventilation using a Fabius Tiro anesthesia workstation (Dräger Medical GmbH, Lubeck, Germany). Intra-abdominal pressure was kept below 13 mmHg during operation. Neuromuscular blockade was reversed with 0.5 mg of glycopyrrolate and neostigmine 2.5 mg at the end of surgery, which lasted for 50 minutes. Patient was extubated after he was fully awake and responding well to verbal commands. He was subsequently allowed oral fluids 4 hours after the end of surgery.

Postoperative analgesia was maintained with intramuscular diclofenac sodium and pentazocine while hydration was optimized with normal saline and 5% dextrose. Serum bilirubin and liver function tests were followed up daily for the next 2 days. Bilirubin settled down to 3.5 mg/dl on

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the second day. He was discharged on day 3 with standing instructions of reporting immediately if jaundice returned or there were symptoms like pain in the abdomen with malaise. His follow-up at 1 week, and subsequently at 1 month, was uneventful.

Discussion

Gilbert's syndrome is a form of hereditary non-hemolytic jaundice; it is transmitted by autosomal dominant pattern.[4] A good understanding of the pathophysiology and precipitating factors of Gilbert's syndrome is needed for safe administration of anesthesia. Surgery and anesthesia are stressful events, thus there is a possibility that bilirubin may increase postoperatively.[5] Although Gilbert's syndrome has been recognized as an important cause of postoperative jaundice, reabsorption of big hematoma and blood transfusion remain as the most important causes of postoperative jaundice.

Many drugs are metabolized or biotransformed by various enzymes, including glucuronyl transferase, in the liver. Gilbert's syndrome can potentially cause such drugs, which utilize these enzymes for its metabolism and ultimate excretion, to accumulate and lead to adverse outcome.

Gilbert's syndrome is diagnosed clinically by its features, precipitating factors, duration of disease. Diagnosis is confirmed by giving phenobarbital which relieves the jaundice and IV nicotinic acid which aggravates it.[6] The jaundice is usually mild (bilirubin less than 6 mg/dl) and other liver function tests are normal. It has been found that women taking oral contraceptive pills do not have symptoms as sex hormones induce this enzyme.[7] For the same reason pregnancy seems to have protective effect. This might explain the male preponderance. It is obvious that relative deficiency of glucuronyl transferase[4] would increase the level of unconjugated bilirubin in the blood producing clinical jaundice which is visible only when the bilirubin is more than 3 mg/dl in the serum.[2]

Any stress can aggravate the symptoms of Gilbert's syndrome e.g., fasting,[8] surgery, infection, exercise, fatigue, alcohol intake and menstruation.[9] Symptoms can range from clinical jaundice to nausea, malaise and discomfort in the right hypochondrium or even abdominal pain. Since fatty acids compete with unconjugated bilirubin in the liver, any period of prolonged fasting can induce symptoms. Postoperative jaundice in patients undergoing oral surgery due to the stress of reduced caloric intake has also been reported.[10]

To avoid prolonged fasting, we kept this patient first on the list. To overcome stress on the night before surgery alprazolam was prescribed. Although lorazepam clearances have been reported to be 20-40% lower in Gilbert patients when compared with controls[11] there is no evidence of any adverse effect of single-dose alprazolam premedication. Five percent dextrose was started early on the morning of surgery to avoid dehydration and hypoglycemia induced stress. It was converted to a normal saline drip intra-operatively as literature has already established that the stress of surgery and anesthesia results in hyperglycemia due to increased secretion of counter-regulatory hormones like catecholamines, cortisol, glucagon and growth hormone.[12]

Propofol was chosen over thiopentone or ketamine as it is metabolized by both liver and kidney providing a safety margin. Besides, thiopentone and ketamine alter liver functions in a dose-dependent fashion.[13,14] Ascertaining the causes of postoperative jaundice therefore becomes difficult.

Fentanyl was considered safe as its effect, after a single bolus dose, is terminated by redistribution to muscle and fat. Subsequent metabolism is primarily by N-dealkylation to norfentanyl and its hydroxylation along with norfentanyl.[15] Remifentanil is a safer alternative due to its ultra-short duration of action and its metabolism by blood and tissue esterase. Although there is no evidence in reported literature about prolongation of other muscle relaxants despite the widespread prevalence of Gilbert's syndrome,[2] atracurium was preferred due to its Hofmann degradation and ester hydrolysis. Mivacurium and Cisatracurium could have been the other safer alternatives due to its similar metabolic pathway.

Isoflurane was considered safer (<0.2% metabolized by liver)[16] as it preserves the liver blood flow. Diclofenac sodium and pentazocine were used for postoperative analgesia. Paracetamol and morphine were specifically avoided. Although paracatamol is not metabolized by glucuronyl transferase,[12] it is metabolized by another enzyme, also deficient in some cases of Gilbert's syndrome[17,18] making these patients susceptible to the potential risk of paracetamol toxicity.[19] Morphine can also exert prolonged effect in Gilbert's syndrome as it is metabolized by conjugation in the liver utilizing the enzyme deficient in these cases.[20]

Being the commonest hereditary cause of increased bilirubin and its widespread prevalence, anesthesia can be safely administered in Gilbert's syndrome provided implications of relative deficiency of glucuronyl transferase on metabolism and excretion of drugs are well understood. To prevent adverse outcome, we should aim should to specifically avoid perioperative stress and ensure adequate hydration.

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