

## CASE REPORT

# Gilbert's syndrome

Alka Chandra, MD, DNB (Anaesth), MBA (Hospital Management)\*, Jayant Nagesh Banavaliker, MD\*\* and R Madhubala Dixit, MD\*\*\*

\*Senior Specialist Hindurao Hospital & Head of Dept, RBIPMT, New Delhi (India)

\*\* Consultant and Head, Department of Chest & T.B, RBIPMT, New Delhi (India)

\*\*\*Consultant and Head, Department of Anaesthesiology, Hindurao Hospital, New Delhi (India)

Correspondence: 802, South Delhi Apartment, Sector 4, Dwarka, New Delhi-110075; Phone; 9560044454; e-mail: dralkadelhi@yahoo.co.in

## ABSTRACT

Gilbert's syndrome is a form of hereditary non-hemolytic jaundice transmitted by autosomal dominant pattern. Since there is low glucuronyl transferase activity in the liver there is a risk for anesthetic toxicity with a possibility of a catastrophic outcome. It is important for the anesthesiologists to understand the pathophysiology of the disease and the conditions leading to decreased glucuronyl transferase activity. We report a case of Gilbert's syndrome with hypertension, operated for cholelithiasis under thoracic epidural analgesia supplemented with transcutaneous electrical nerve stimulation in the postoperative period. Minimal administration of intravenous drugs, maintaining the organ perfusion and postoperative pain relief using epidural anesthesia offers a safe conduct of anesthesia which can be considered as an alternative to general anesthesia.

**Key words:** Gilbert's syndrome; Glucuronyl transferase; TENS

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## INTRODUCTION

Gilbert's syndrome is characterized by mild unconjugated hyperbilirubinemia, but normal values for standard hepatic biochemical tests and normal hepatic histology other than a modest increase of lipofuscin pigment in some patients. Serum bilirubin concentrations are most often <3mg/dl although both higher and lower values are frequent. More elevated values are associated with stress, fatigue, alcohol use, reduced caloric intake and concomitant illness.<sup>1</sup> Gilbert's syndrome patients required proper evaluation; surgery should be performed as a first case in the morning to minimize fasting and waiting stress. Glucose infusion should be started before surgery and adequate postoperative analgesia should be achieved to reduce the stress in addition to avoiding or reducing the use of drugs that are metabolized or biotransformed by glucuronyl transferase in the liver.<sup>2</sup> We present a case report of this syndrome with hypertension which posed several challenges to the anesthesiologists.

## CASE REPORT

A 43 years old male, weighing 65kg, was posted for

elective cholecystectomy. He was diagnosed to be suffering from Gilbert's syndrome few years back. He gave the history of recurrent jaundice with illness and stress which resolved subsequently without any medical intervention. Six months back he was started with tab. amlodipine besylate (Norvasc®) 2.5 mg for hypertension. On physical examination he looked icteric. His liver function tests before surgery revealed total bilirubin to be 3.6mg/dl with the unconjugated fraction as 3.1mg/dl; aspartate aminotransferase and alanine transaminase to be 48 IU/L and 56 IU/L respectively. The alkaline phosphatase was increased at 80 IU/L. The total protein and the albumin levels were normal. The peripheral smear and reticulocyte count were done to rule out any component of hemolysis. The INR was 1.4, kidney functions were normal and viral markers showed no abnormality. The patient was given tab. alprazolam 0.5 mg on the night before surgery to reduce the stress, and was taken as the first case in the morning. 5% dextrose was started in the morning and the morning dose of antihypertensives was given with a sip of water. In the operating room the fluid was changed to lactated Ringer's solution. Since there was a palpable lump and the surgeons were suspecting excessive adhesions at the

site, an open cholecystectomy was planned. Standard monitoring with five lead electrocardiogram, oxygen saturation and non-invasive blood pressure monitoring were established. Pre-operative vital signs were pulse 88/ min, blood pressure 140/92 mmHg and SpO<sub>2</sub> of 98% on room air. Thoracic epidural anesthesia was planned; however, all the drugs for general anesthesia were kept ready in case the surgeon or the patient became uncomfortable. Under all aseptic precautions the epidural space was localized using loss of resistance technique with air. Epidural catheter was inserted in T8-9 space through 16G Tuohy's needle. A length of 3-4cms of the catheter was left in the epidural space. A test dose with 3 ml of 2% lignocaine with adrenaline was given followed by bolus of 14 ml of 0.5% bupivacaine mixed with 50 µg of inj. fentanyl after adequate preloading. The operation took 60 min. Oxygen supplementation was done with the face mask to maintain optimum saturation. The relaxation as well as the analgesia were optimum. The blood sugar and liver function tests were repeated after the procedure which did not show any significant change from the pre-operative values. In the postoperative period transcutaneous electrical nerve stimulation (TENS) was applied for 45 min at a constant frequency of 80 Hz for pain relief. The patient complained of some discomfort after 8 hrs of surgery and 10 ml of 0.125% of bupivacaine was loaded. No other analgesic was required by the patient. There was a minimal rise in the bilirubin level on the next day with total bilirubin of 4.2 mg/dl and indirect bilirubin of 3.5 mg/dl, with no significant changes in the enzyme levels. On the subsequent days the bilirubin levels came down to 2.8 mg/dl and 2.2 mg/dl. The patient was discharged on day 5. His follow up after one week and at one month was uneventful.

## DISCUSSION

Gilbert's syndrome is an inherited disorder of hepatic bilirubin metabolism occurring in the population with a frequency range from 2-13%.<sup>3</sup> It causes a mild chronic unconjugated hyperbilirubinemia in otherwise healthy people. Screening for liver disease or hemolysis reveals no pathological finding, but the hepatic glucuronidation capacity is reduced by 70%.<sup>4</sup> It is caused by a mutation of the specific UDP glucuronyl transferase conjugating bilirubin with glucuronic acid resulting in a reduced activity of this enzyme. It is crucial to establish a correct diagnosis and differentiate this syndrome from serious disorders of the liver tissue.<sup>5</sup> Any stress can aggravate the symptoms of Gilbert's syndrome e.g. prolonged fasting, surgery, infection, exercise, fatigue, alcohol intake and menstruation.<sup>6</sup> Administration of

phenobarbitone normalizes both the serum bilirubin concentration and hepatic bilirubin clearance; however failure of UGT1A1 activity to improve in many instances suggest the possible coexistence of an additional defect.<sup>1</sup> Rifampicin test and caloric restriction test are two non-invasive diagnostic means to diagnose Gilbert's syndrome with the benefit of avoiding hazardous liver biopsy.<sup>7</sup>

Fentanyl is 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.<sup>8</sup> Paracetamol and morphine are avoided, although paracetamol is not metabolized by glucuronyl transferase it is metabolized by another enzyme also deficient in some cases of Gilbert's syndrome making these patients susceptible to the potential risk of paracetamol toxicity. Morphine can also exert prolonged effect in Gilbert's syndrome as it is metabolized by conjugation in the liver.<sup>9</sup> Since general anesthesia requires a lot of intravenous medications in addition to inhalational anesthetics, it was decided to go for thoracic epidural anesthesia. However, the drugs known to be safe were kept ready in case they would be required. Surgery leads to stress response characterized by sympathetic stimulation, altered balance of catabolic and anabolic hormones, hypermetabolism, negative protein economy and altered carbohydrate metabolism and immune function. A three-fold increase of the plasma level of norepinephrine was detected upto 24 hrs after surgery. Thoracic epidural analgesia provides optimal perioperative anesthesia and analgesia after thoracic and major abdominal surgery and decreases postoperative morbidity and mortality mainly by blocking sympathetic nerve fibres. It reduces postoperative pulmonary complications as compared to anesthesia and analgesia without epidural anesthesia.<sup>10,11</sup> The blood levels of local anesthetics is determined by the rate of uptake, tissue redistribution, metabolism and excretion. The rate of vascular absorption is a function of the site of injection, dosage etc. The aminoamides are metabolized primarily in the liver. Bupivacaine is cleared more slowly due to its decreased rate of hepatic degradation.<sup>12</sup> Decreased hepatic blood flow or impaired hepatic enzyme function can produce substantially elevated levels of the aminoamide local anesthetics.<sup>13</sup> However in a study by A. Kortgen,<sup>14</sup> it was found that thoracic but not lumbar epidural anesthesia increases liver blood flow after major abdominal surgery.

TENS has also been applied in the postoperative period for pain relief. It has been proven by Chandra et al<sup>15</sup> that TENS can be used as an adjunct to epidural analgesia for acute postoperative pain without

causing any squeals in addition to stabilizing the hemodynamics. The mechanism by which TENS produces analgesia is unclear and may be related to the modulation of nociceptive impulses in the spinal cord, release of endogenous endorphins and enkephalins or a combination of these and other mechanisms.<sup>16</sup> Although in a case report general anesthesia was safely given with fentanyl, propofol, atracurium and maintained with isoflurane, oxygen and nitrous oxide;<sup>2</sup> remarkable perioperative complications have also been reported after general anesthesia. Alarming levels of bilirubin in the postoperative period requiring plasmapheresis for 4 days have been reported.<sup>17</sup>

In our case since the patient was hypertensive we decided to go for thoracic epidural anesthesia for better control of hemodynamics. Many beneficial effects of epidural anesthesia and analgesia have been demonstrated as discussed during perioperative period including attenuation of surgical stress response, effective pain

relief, faster recovery of gut function, reduction in postoperative thrombo-embolic and cardio-respiratory complications.<sup>18</sup> To avoid stress of fasting the patient was taken in the morning and adequate precautions were taken to avoid hypoglycemia induced stress. Preloading was done with Ringer's lactate solution to avoid any episode of hypotension. TENS was added in the postoperative period to avoid the use of narcotics for adequate pain relief to avoid any kind of stress.

## CONCLUSION

Although general anesthesia can be administered in Gilbert's syndrome taking into account the implications of relative deficiency of glucuronyl transferase on metabolism and excretion of drugs, epidural anesthesia and analgesia in addition to TENS in the postoperative period for pain relief can offer an excellent alternative in the anesthetic management of Gilbert's syndrome.

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