Perioperative management and anaesthetic considerations for adult patients with Gilbert’s syndrome and oral cancer: review and case report

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ABSTRACT
Gilbert’s syndrome is the most common cause of hereditary hyperbilirubinemia and poses a clinical challenge for anaesthesiologists. The decreased activity of bilirubin uridine glucuronyl transferase can lead to toxicity for usual doses of most anaesthetic agents. We review and discuss the approach to successful and safe anaesthesia management in these patients and we report a case of a 48-year-old male patient with Gilbert’s syndrome submitted to maxillofacial surgery under general anaesthesia. The recommended approach for the most successful and safe anaesthesia management in such patients includes the following: (i) minimizing the period of fasting to avoid hypoglycemia and dehydration; (ii) decreasing the perioperative stress by providing anxiolysis and adequate analgesia; (iii) avoiding hepatotoxic drugs and drugs predominantly metabolized by the liver; (iv) maintaining the hepatic blood flow; and (v) reduce polypharmacy.

ARTICLE HISTORY
Received 13 April 2019
Accepted 26 July 2019

KEYWORDS
Gilbert’s syndrome; anaesthesia; oral cancer; maxillofacial surgery

Introduction
Gilbert’s syndrome (GS), first described in 1901 [1], is the most common inherited disorder of bilirubin metabolism leading to decreased glucuronidation of bilirubin. GS is a mild, chronic, unconjugated hyperbilirubinemia (less than 6 mg/dL) occurring in the absence of overt hemolysis or any other evidence of liver disease [2–4]. The reported incidence of GS is between 3 and 10% in the general population depending on differences in how it is defined and diagnosed [5, 6]. It is more common in men than in women, and is typically first diagnosed during a person’s late teens or early twenties [7].

Anaesthesia management for patients with hepatic dysfunction can be quite challenging, as many anaesthetic agents are metabolized by the liver [8–11]. GS is associated with lack of detoxification of some drugs (including anaesthetic agents) and possible intraoperative toxicity. A good understanding of the pathophysiology and precipitating factors of GS is needed for safe administration of anaesthesia.

This article reviews the literature on the anaesthetic management in patients with GS and presents the case of a patient with GS and tongue cancer who was submitted to elective maxillofacial surgery under general anaesthesia.

Overview of Gilbert’s syndrome
Gilbert’s syndrome is a genetic liver condition (with autosomal-recessive inheritance) characterized by a defect in the gene that encodes the conjugating enzyme uridine diphosphate glucuronyltransferase 1A1 (UGT1A1). UGT1A1, is first and foremost expressed in the liver, where it is the main bilirubin glucuronidation enzyme [12–14]. The inherited defect in uridine glucuronyltransferase (UGT) production results in a 60–70% reduction in the liver’s ability to conjugate bilirubin and causes a mild chronic non-haemolytic, intermittent unconjugated hyperbilirubinemia in otherwise healthy people [2, 3, 5]. Since UGT is involved in drug metabolism, a GS individual is more likely to experience drug toxicity.

About 30% of the cases are asymptomatic, although nonspecific symptoms, such as abdominal discomfort, fatigue and malaise, are not uncommon [15]. Jaundice, the only symptom that can be definitely associated with GS, is usually triggered by any

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Diagnosis of Gilbert’s syndrome

Usually, GS is the diagnosis of exclusion. GS may be diagnosed by medical history, duration of the disease, lack of overt hemolysis or other liver diseases justifying jaundice and jaundice triggered by predisposing factors [7, 8]. Most commonly performed haematology and serum biochemical assays (with the exception of unconjugated hyperbilirubinemia), as well as liver biopsy are normal. Diagnosis may be confirmed by jaundice improvement after phenobarbital [3, 13] and worsening after intravenous nicotinic acid and caloric restriction [7, 13]. Nowadays the method of choice in the diagnostics of GS is a genetic verification of disorder [4, 17, 18]. The genetic basis of GS was first identified in 1995 after the discovery of the A(TA)7TAA mutation [13, 14]. The promoter of the UGT1A1 gene is amplified by polymerase chain reaction to identify a genetic defect in the enzyme [19]. This test is a quick and accurate method for confirming a diagnosis.

Perioperative drug management

The deficiency of the enzyme UGT in GS affects the drug glucuronidation and as majority of the anaesthetic agents are metabolized in the liver, it could potentially precipitate unexpected toxicity [2, 7, 20]. Perioperative management in patients with GS can be quite challenging [21]. It is important for the anaesthesiologist to understand the pathophysiology and conditions leading to decreased UGT activity in GS patients submitted to anaesthesia and surgery, to prevent intraoperative toxicity and to administrate safe anaesthesia. Perioperative goals in such patients are (i) minimizing the period of fasting to avoid hypoglycemia and dehydration; (ii) decreasing the perioperative stress by providing anxiolysis and adequate analgesia; (iii) avoiding hepatotoxic drugs and drugs predominantly metabolized by the liver; (iv) maintaining the hepatic blood flow; and (v) reducing polypharmacy.

To provide adequate analgesia during the intraoperative period, opioids are used. Among them, fentanyl is seen as an appropriate choice, because it is considered to be safe as it is metabolized in the liver by CYP3A4 primarily to norfentanyl (>99%) and other inactive metabolites, and its effect, after a single bolus dose, is terminated by redistribution to muscle and fat [22]. Prolonged duration of the effect of fentanyl would appear unlikely but in some cases, it may be reasonable to use a small dose. Remifentanil is a safer alternative due to its ultra-short duration of action and as an ester is degraded by plasma and tissue esterases [8], thus preventing liver function impairment. On the other hand, it needs to be supplemented with longer acting opioids at the end of the surgery to avoid a complicated emergence due to pain. Morphine is predominantly cleared by glucuronidation and consequently can also exert prolonged effects; although there is a report about lack of effect on morphine pharmacokinetics in GS patients, and that there is no need to modify its dose [23].

All inhaled anaesthetics decrease the total liver blood flow and this decrease is maximum with halothane and minimum with isoflurane [24, 25]. The hepatic metabolism is highest with halothane (15–40% of drug), followed by enflurane (2.4%), sevoflurane (2–5%), isoflurane (<0.2%) and desflurane (0.02%) [8, 26]. Thus, isoflurane was considered safer as it better preserves the hepatic blood flow and function [10].

The neuromuscular blocking agent of choice will be atracurium, due to its Hofmann degradation and ester hydrolysis. Mivacurium and cis-atracurium could be other safer alternatives due to their similar metabolic pathway. Vecuronium and rocuronium, both steroid-based neuromuscular blockers, have a prolonged elimination phase in severe liver disease and are, therefore, not recommended [9].

It is advisable to use regional anaesthesia where appropriate and bupivacaine is the preferred agent.

Case report

A 48-year-old male patient (body weight 84 kg) diagnosed with histologically confirmed tongue cancer (carcinoma in situ and high-grade oral epithelial dysplasia, cpTis) was presented to us for elective maxillofacial surgery. He had a history of GS (diagnosed at the age of 18), which was confirmed once more before surgery by detecting a mutation in the promoter region of the UGT1A1 gene using direct DNA
sequencing (the assay was performed in the Molecular Medicine Center, Medical University, Sofia, Bulgaria). The DNA samples were obtained for analysis and storage with written informed consent. UGT1A1 DNA sequence was searched against the National Center for Biotechnology Information (NCBI) database. Primers were designed using the online primer design software, Primer 3, according to published UGT1A1 sequences. The patient was found to be homozygous for the UGT1A1*28 variant, A(TA)7TAA allele, which has been associated with decreased glucuronidation. This variant has the highest frequency among patients with clinically recognized GS. Routine laboratory investigations were within the normal range, including the serum bilirubin levels (total bilirubin of 16.5 µmol/L with a unconjugated fraction of 10.6 µmol/L; normal value up to 21.0 µmol/L and up to 15.0 µmol/L, respectively) and the liver function tests (aspartate aminotransferase and alanine transaminase 21.0 and 27.8 IU/L, respectively). Hepatitis viral markers were negative. The patient was assessed under ASA (American Society of Anaesthesiologists) physical status II and was accepted for general anaesthesia with added risk [27]. The patient was scheduled first on the list. He was premedicated with midazolam 2.0 mg and omeprazole 40 mg intravenously (IV) on the morning of the surgery and a 5% dextrose drip was started. In the operating room, the fluid was changed to lactated Ringer’s solution drip at the start of surgery as maintenance fluid. Intraoperative monitoring was done as per ASA standards [28]. Preoperative vital signs were as follows: pulse 83 bpm, blood pressure 120/80 mmHg and oxygen saturation (SpO2) 98% on room air. After preoxygenation with 100% oxygen for 3 minutes and IV fentanyl 100 µg, anaesthesia was induced with IV propofol 200 mg and 100 mg suxamethonium to facilitate intubation of the trachea (size 8.0-cuffed endotracheal tube), followed by IV fentanyl 100 µg and atracurium 40 mg when ventilation resumed. Pharyngeal packing was done to prevent trickling of blood into the pharynx. General anaesthesia was maintained with isoflurane, air and oxygen (50:50) through the circle system and intermittent positive pressure ventilation using a Dräger Fabius GS anaesthesia workstation (Germany) to achieve a MAC of 1.0. Intravenous metoclopramide 10 mg as an antiemetic drug and dexamethasone 8 mg for decreasing postoperative oedema were administered prior to the surgery onset. The intraoperative period was uneventful with stable hemodynamics (mean arterial pressure above 60 mmHg). The surgery lasted 45 minutes and tumour excision was done. The patient was extubated, once he had adequate respiratory efforts and tidal volume, and was fully awake and responding well to verbal commands. Postoperative analgesia was maintained with IV dexketoprofen trometamol (50 mg) started 15 minutes before the end of the surgery, and then applied on regular basis, while hydration was optimized with lactated Ringer’s solution and 5% dextrose. Oral intake of fluids was resumed on day 1 after the operation and after another 3 days, the patient was able to manage a pureed diet. Early oral feeding was not associated with any adverse events. Serum bilirubin and liver function tests were repeated after the surgery, which did not show any significant changes from the preoperative values. Postoperative recovery was satisfactory and the patient was discharged home on day 5 with standing instructions of reporting immediately any complaint. His follow-up after one week and at one month was uneventful.

Anaesthetic considerations

In the case of our patient, general anaesthesia was planned. Avoiding use of hepatotoxic drugs and drugs that are predominantly metabolized by the liver is of primary importance. We decided to take an approach using as few drugs as possible that have short duration of action and extrahepatic metabolism.

The patient’s operation was scheduled first in the morning, and a 5% glucose solution was infused early on the morning of surgery to avoid dehydration and hypoglycemia induced stress, as they are known jaundice triggering factors. Hydration during surgery was achieved by lactated Ringer’s solution, since it is already well defined that surgery is associated with increased glycemia as a neuroendocrine metabolic response. To minimize preoperative stress, short-acting benzodiazepine was used to achieve anxiolysis before surgery.

Fast track induction using propofol and suxamethonium with subsequent endotracheal intubation was chosen to minimize the risk of failure. Propofol was preferred over thiopental or ketamine, as it is metabolized by both the liver and the kidneys providing a safety margin and as well as due to its least adverse effects on hepatic blood flow. Furthermore, thiopental and ketamine affect liver function tests depending on the dose, and etomidate may lead to adrenal failure [9]. We preferred to use isoflurane over other volatile agents for anaesthesia maintenance for our patient.

We chose dexketoprofen trometamol for postoperative analgesia. Paracetamol should be avoided because of drug toxicity, as it is metabolized by another
enzyme (other than UGT) also deficient in some people with GS [29].

The following factors could be the possible crucial points for provoking jaundice in patients: anxiety and fasting before surgery with risk of hypoglycemia induced stress; hemodynamic instability with low blood pressure (mean arterial pressure <60 mmHg) during surgery; pain and reduced oral intake after surgery, as well as hematoma formation at the site of the operation. In our patient, however, no jaundie was observed perioperatively.

In our case, the anaesthesia for the maxillofacial surgery was uneventful with emphasis on adequate premedication (including anxiolysis), early operation in the morning to minimize preoperative starvation and avoiding hypoglycemia induced stress by infusing 5% dextrose solution, as well as preloading with Ringer lactate solution to avoid any episode of hypotension. General anaesthesia was safely given with fentanyl, propofol, atracurium and maintained with isoflurane, oxygen and air. The intraoperative period was uneventful with stable hemodynamics. Remarkable perioperative complications were not observed.

Conclusions

Gilbert’s syndrome is the most common cause of hereditary hyperbilirubinemia and poses a clinical challenge for anaesthesiologists. The decreased activity of bilirubin-UGT can lead to toxicity of the usual doses of most anaesthetic agents. A good understanding of the pathophysiology and precipitating factors of GS is needed for safe administration of anaesthesia. Avoiding prolonged fasting and perioperative stress, maintenance of adequate hydration, use of short acting drugs or such with extra hepatic metabolism are the key to the successful and safe management of patients with GS.

Acknowledgment

The authors declare that the material has not been published before.

Disclosure statement

No potential conflicts of interest were disclosed.

Ethics statement

Written informed consent was obtained from the patient.

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