

Anesthesia and Airway Management of Pediatric Patients with Smith-Lemli-Opitz Syndrome

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SMITH-LEMLI-OPITZ syndrome (SLOS) is an autosomal recessive disorder with an incidence of between 1 in 26,500 pregnancies in Canada and 1 in 50,000 pregnancies in the United States.^{1,2} The syndrome results from an inborn error of cholesterol biosynthesis involving a deficiency of 3β -hydroxysterol Δ^7 -reductase, the enzyme that catalyzes the reduction of 7-dehydrocholesterol to cholesterol.^{3,4} As a result, patients with SLOS have abnormal embryonic development, high plasma concentrations of 7-dehydrocholesterol, and usually decreased plasma concentrations of cholesterol.

This biochemical defect is associated with a broad spectrum of clinical manifestations with potentially profound anesthetic implications. Patients with SLOS can have severe growth failure, congenital anomalies affecting most organ systems, early death, developmental delay, and self-injurious and ritualistic behavior.⁵⁻⁹ Of special concern to anesthesiologists are the typical dysmorphic facial features, including micrognathia, cleft palate, and a small and abnormally hard tongue, which can present a challenge in airway management of patients with SLOS.^{5,8}

The broad spectrum of congenital anomalies and potential increase in lifespan with dietary cholesterol replacement therapy make it very likely that diagnostic and therapeutic interventions requiring anesthesia will be needed in patients with SLOS. However, since the discovery of the biochemical defect in SLOS, little has been reported on the anesthetic management of these pa-

tients.¹⁰ In this report, we describe the administration of 20 anesthetics in 14 patients with confirmed biochemical diagnosis of SLOS. Our focus was on airway management, and because of previous reports of difficult intubations in some of our patients, we chose to use fiberoptic laryngoscopy as the initial technique to achieve tracheal intubation.

Report of Cases

We reviewed the anesthetic management of 14 children who were enrolled in ongoing investigations of the clinical, molecular, and biochemical features of SLOS and received 20 general anesthetics from July 2000 to February 2002. The investigation protocol was approved by the National Institutes of Child Health and Development Institutional Review Board. Clinical diagnosis was confirmed biochemically in all patients (table 1).

Demographics, including the SLOS severity score¹¹ of the 14 children, are listed in table 1. Additional details on the patients and anesthetics reported here are available on the ANESTHESIOLOGY Web site, <http://www.anesthesiology.org>. Figure 1 depicts a 9-month-old infant with SLOS and features of Pierre Robin sequence (micrognathia, glossoptosis, and high-arched and cleft soft and hard palates) who was anesthetized at 3, 9, and 15 months of age. Six patients had a history of gastroesophageal reflux predominantly associated with feedings (table 1). However, once on metoclopramide, H₂ blocker, and H⁺-K⁺ ATPase inhibitor, these patients had no clinical signs of gastric reflux. In addition, despite the history of gastric reflux, no episode of aspiration pneumonia was recorded in any of our patients. Eight patients had gastric tubes through which they were fed exclusively (table 1). Patient 9 had a history of hypertension that was treated with a calcium channel blocker. Five patients (table 1) had a documented history of difficult intubation, as described by anesthesiologists who had previously performed direct laryngoscopies. In patient 9, a previous anesthetic was aborted because we were unable to intubate after induction of anesthesia.

In this series, one anesthesiologist administered all of the anesthetics and performed all of the endotracheal intubations, with the exception of one (table 2). All patients had solids or formula discontinued 8 h before induction of anesthesia, but clear liquids were allowed for up to 3 h before induction of anesthesia. Only patient 4, an 8-yr-old boy with aggressive behavior, required premedication with oral midazolam (0.4 mg/kg) and ketamine (10 mg/kg), which yielded effective sedative effects. In patients with gastric tubes, the stomach was emptied immediately prior to induction of anesthesia.

The ability to mask ventilate was established, and intravenous access was obtained. One patient had intravenous induction with sodium thiopental. All patients had documented easy mask ventilation without oropharyngeal airways. During fiberoptic laryngoscopy and endotracheal intubation, most patients were spontaneously ventilating, and the inspired concentration of oxygen was increased to 100%. Overall, during induction of anesthesia and tracheal intubations, oxygen saturation was maintained above 99% in all patients. In two patients (patients 2 and 13), mivacurium was given just prior to the insertion of the endotracheal tube in the trachea. Succinylcholine was administered to treat one episode of laryngospasm that was evident during

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Table 1. Demographics, Congenital Anomalies, and Diagnostic Plasma Sterol Levels in a Series of Patients with Smith-Lemli-Optiz Syndrome

Patient (Gender)	Age* (mo)	Weight, Kg (percentile)	Severity Score†	Congenital Heart Disease	GERD	Gastric Tube	Hypotonia	Cleft Palate	Micrognathia	Plasma Sterol Levels (normal values, mg/dL)	
										Cholesterol (100–200)	7-DHC (0.01 ± 0.005)
1 (F)	7	5 (<3 rd)	28	PDA	Y	Y	Y		Y	56	27.3
2 (F)	29	10 (<3 rd)	17	PDA, Aorta coarctation		Y	Y		Y	70	13.5
3 (M)	13	8 (<3 rd)	11	Pulmonary stenosis			Y		Y	65	12.6
4 (M)	96	25 (50 th)	11							195	0.07
5 (M)	18	7 (<3 rd)	6				Y		Y	89	12.2
6 (M)	4	6 (25 th)	11		Y	Y	Y		Y	72	8.5
7 (F)	3	3 (<3 rd)	33		Y		Y	Y	Y	8	23.7
8 (M)	9	6 (<3 rd)	6			Y	Y		Y	36	12.8
9 (F)	25	6 (<3 rd)	31	ASD		Y	Y		Y	83	15
10 (M)	27	10 (<3 rd)	6				Y		Y	114	5.4
11 (M)	8	7 (<3 rd)	33		Y	Y	Y		Y	31	13.9
12 (F)	11	5 (<3 rd)	11		Y	Y	Y		Y	20	7.8
13 (M)	39	12 (3 rd)	11				Y		Y	73	6.2
14 (F)	26	8 (<3 rd)	39	ASD	Y	Y	Y	Y	Y	21	13.7

* Age at the first anesthetic in this series. † Severity scores are based on the presence of malformations in each of 10 embryologically distinct areas.¹¹ Scores greater than 50 reflect severe disease, 25–50 reflect moderate or typical disease, and less than 25 reflect mild disease.

F, female; M, male; PDA, patent ductus arteriosus; ASD, atrial septal defect; GERD, gastroesophageal reflux disease; Y, yes (showing that the characteristic is present).

fiberoptic laryngoscopy (patient 5). All endotracheal intubations were electively performed with fiberoptic bronchoscopes (model BF-XP40 [outside diameter, 2.8 mm] for endotracheal tubes sized 3.5 or above and model LF-P [outside diameter, 2.2 mm] for those sized 3 and below, Olympus America, Melville, NY). In patients undergoing oral and dental examinations (six anesthetics), the endotracheal tube was inserted nasally, whereas in those undergoing only imaging studies, it was inserted orally (14 anesthetics). We used cuffed endotracheal tubes for 8 anesthetics and uncuffed tubes for the remaining 12 anesthetics. Most children required a smaller sized endotracheal tube than that predicted for their age (table 2).

In 19 anesthetics, fiberoptic laryngoscopy was the technique chosen for tracheal intubation from the outset. In one anesthetic, four direct laryngoscopies were performed, and an otolaryngologist was consulted to perform indirect laryngoscopy and thereby intubate the

trachea. All intubations were performed successfully and without trauma to the airway. The agents used in the maintenance phase of the anesthetics are listed in table 2. At the completion of all procedures, the patients were extubated. Only patient 7, when administered the first anesthetic, presented airway obstruction after extubation that was relieved with a nasopharyngeal airway. There were no episodes of oxygen desaturation, bradycardia, witnessed aspiration, or aspiration pneumonia.

Discussion

Given the relatively high incidence, presence of multiple congenital malformations, expansion of the pheno-

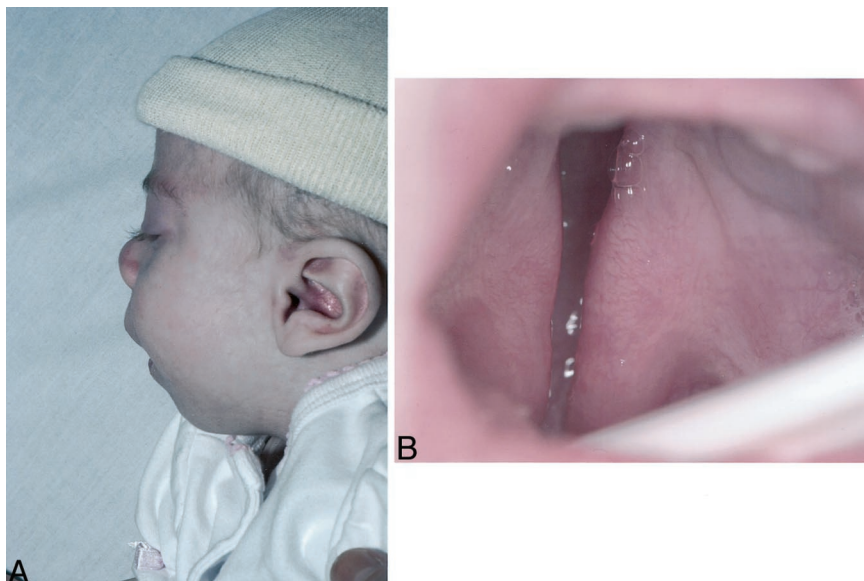


Fig. 1. (A) Nine-month-old infant with Smith-Lemli-Optiz syndrome presenting features associated with Pierre Robin sequence, including micrognathia, cleft palate (B), and pseudomacroglossia.

Table 2. Series of 20 Anesthetics in Patients with Smith-Lemli-Optiz Syndrome

Patient	History of Difficult Intubation*	Procedures	Induction Agents	Endotracheal Tube Size	Maintenance Agents	Comments
1	Y	Eye muscle surgery	Thiopental Vecuronium	3.5 Uncuffed	N ₂ O, Desflurane	Tracheal intubation by an otolaryngologist
1	Y	Brain MRI, spectroscopy	N ₂ O, Sevoflurane	3.5 Uncuffed	N ₂ O, Isoflurane	
1	Y	Brain MRI, spectroscopy	N ₂ O, Sevoflurane	3.5 Uncuffed	N ₂ O, Propofol	
2		Brain MRI, spectroscopy	N ₂ O, Sevoflurane	4.0 Uncuffed	N ₂ O, Isoflurane	
3		Brain MRI, spectroscopy Dental rehabilitation	N ₂ O, Sevoflurane	4.0 Uncuffed	N ₂ O, Isoflurane	
4		Brain MRI, spectroscopy	N ₂ O, Sevoflurane	5.0 Cuffed	N ₂ O, Isoflurane	
5		Brain MRI, spectroscopy	N ₂ O, Sevoflurane	4.0 Uncuffed	N ₂ O, Propofol	Laryngospasm during intubation
6		Brain MRI, spectroscopy	N ₂ O, Sevoflurane	3.5 Uncuffed	N ₂ O, Propofol	
6		Brain MRI, spectroscopy	N ₂ O, Sevoflurane	3.5 Cuffed	N ₂ O, Propofol	
7	Y	Brain MRI, spectroscopy	N ₂ O, Sevoflurane	3.0 Uncuffed	N ₂ O, Isoflurane	
7	Y	Brain MRI, spectroscopy	N ₂ O, Sevoflurane	3.0 Uncuffed	N ₂ O, Isoflurane	
7	Y	Brain MRI, spectroscopy eye EUA	N ₂ O, Sevoflurane	3.5 Uncuffed	N ₂ O, Propofol	
8		Brain MRI, spectroscopy	N ₂ O, Sevoflurane	3.5 Uncuffed	N ₂ O, Propofol	
9	Y	Brain MRI, spectroscopy Dental rehabilitation	N ₂ O, Sevoflurane	3.5 Cuffed	N ₂ O, Propofol	Prior procedure cancellation because of inability to intubate
10		Brain MRI, spectroscopy Dental rehabilitation	N ₂ O, Sevoflurane	4.0 Cuffed	N ₂ O, Propofol	
11	Y	Brain MRI, spectroscopy	N ₂ O, Sevoflurane	3.5 Uncuffed	N ₂ O, Propofol	
12		Brain MRI, spectroscopy	N ₂ O, Sevoflurane	3.5 Cuffed	N ₂ O, Propofol	
13		Brain MRI, spectroscopy Dental rehabilitation	N ₂ O, Sevoflurane	4.0 Cuffed	N ₂ O, Propofol	
14	Y	Brain MRI, spectroscopy Dental rehabilitation	N ₂ O, Sevoflurane	3.5 Cuffed	N ₂ O, Propofol	

* Difficult intubation as described by anesthesiologists who had previously performed direct laryngoscopies.

Y, yes; MRI, magnetic resonance imaging.

typic spectrum to include patients with milder cases, biochemical confirmation of the clinical diagnosis, and the use of dietary cholesterol replacement therapy for SLOS, the probability that an anesthesiologist will care for patients with SLOS is likely to increase. However, the literature on the anesthetic management of SLOS is scarce. Since the discovery of the biochemical defect associated with SLOS in 1994, there have been only small case series reported in the literature.^{10,12,13} In this report, we describe a series of 20 anesthetics in 14 patients with biochemically confirmed SLOS. Because of prior history of difficult intubation in 5 of our 14 patients, we prospectively decided to use fiberoptic laryngoscopy as the initial technique for tracheal intubation in the anesthetics described here. We have shown that, in skilled hands, fiberoptic intubation can be performed safely, efficiently, and without complications, and it can be used as an initial technique for airway management in patients with SLOS.

When planning to administer an anesthetic in a patient with SLOS, the anesthesiologist will have to address several issues pertinent to this complex syndrome. First, facial dysmorphic features in patients with SLOS, including those associated with Pierre Robin sequence (micrognathia and palatal anomalies) and prominent incisors, can be associated with difficulties in airway manage-

ment. In the literature, there are several reports of difficult intubation and abnormal laryngoscopic view in patients with SLOS.^{10,13,14} In our institution, we had to abort two procedures because of inability to intubate SLOS patients with direct laryngoscopy. In one patient in our series, an otolaryngologist performed fiberoptic intubation of the trachea after a pediatric anesthesiologist had attempted four direct laryngoscopies. We chose to perform fiberoptic intubation of the trachea as the initial technique for 19 of the anesthetics in this series. We were able to maintain spontaneous ventilation and adequate oxygenation and to intubate all patients without repeated direct laryngoscopies or trauma to the airway. Therefore, our experience suggests that in patients with SLOS, tracheal intubation by fiberoptic laryngoscopy is an excellent alternative for the airway management of these pediatric patients. Evidently, in order to make this a viable alternative, fiberoptic scopes that accommodate endotracheal tubes smaller than size 5.5 are required, and the staff must be trained in the technique of fiberoptic intubation.

Second, the potential for a difficult airway, when associated with the presence of gastroesophageal reflux, can be particularly concerning for the anesthesiologist. Although a common problem in patients with SLOS, gastroesophageal reflux is often a result of the combination

of small stomachs and intestinal dysmotility.⁵ After careful history taking, it was clear that, in most of our patients with SLOS, gastroesophageal reflux was predominantly associated with feedings. We felt that rapid sequence inductions were not warranted. Preoperatively, we prescribed an 8-h fast for formula and 3-h for clear liquids. Those patients on H₂ blockers and metoclopramide were given their doses 3 h prior to their anesthetics. Just prior to induction, we applied gentle suction to the gastric tube in patients who had a gastrotomy. We observed no episodes of regurgitation or aspiration of gastric contents with this regimen. Therefore, our experience with patients with SLOS suggests that if the history indicates that gastroesophageal reflux is predominantly associated with feedings and if strict fasting guidelines are followed, rapid sequence induction may not be necessary in all patients, and inhalation induction can be performed safely.

Another issue that anesthesiologists must keep in mind is the possible association of muscle rigidity and the use of inhalation agents in patients with SLOS. Petersen and Crouch¹² reported a 4-yr-old child with SLOS who exhibited muscle rigidity after the use of halothane. In that case, muscle rigidity was associated with a mild elevation in temperature but no elevation of creatinine kinase concentrations. In our series of 20 anesthetics, all patients received halogenated agents, and no episodes of muscle rigidity were observed. Furthermore, we used succinylcholine in one of these patients without any problems. Although no definitive conclusion can be made, in our experience, the use of halogenated anesthetics in this population was not associated with muscle rigidity.

Behavioral abnormalities are also issues that need to be addressed in the preoperative assessment of patients with SLOS. SLOS is known to be associated with behavioral disorders, including autism. In a study of patients with SLOS, 9 of the 17 patients without hearing deficit (53%) met the diagnostic criteria for autistic disorder, and 50 of 56 (89%) had aggressive behavior that was either self-injurious or directed against others.⁹ In that study, patients younger than 22 months did not show behavioral dysregulation.⁹ In addition, in a large series of patients with documented SLOS, the use of sedatives was reportedly ineffective.⁸ Certainly, such a high incidence of abnormal and aggressive behavior coupled with a lack of response to sedatives can pose a challenge for the pediatric anesthesiologist. In our series, only five anesthetics were administered in children older than 22 months, and only one of these children exhibited aggressive behavior. Although we did not observe any difficulty in sedating or anesthetizing our patients with SLOS, one could postulate that abnormalities of cellular membrane sterol composition in SLOS patients could alter their response to sedatives and anesthetic agents.

Some animal studies support this hypothesis. In a genetic mouse model of SLOS with biochemical and phenotypic

similarities to the human syndrome, the neurophysiologic response of frontal cortex neurons to the excitatory amino acid glutamate was significantly impaired.¹⁵ These findings in animals may suggest that in patients with SLOS, an abnormal sterol cellular membrane composition could impact the physiologic response of neurotransmitters. In turn, these abnormalities could impact the response to sedatives and anesthetic agents. Therefore, it is not surprising that patients with SLOS reportedly have an abnormal response to sedatives.⁸ From a clinical standpoint, all of our anesthetics were rather uncomplicated. However, further studies are needed to fully characterize the neuropharmacologic impact of the biochemical abnormalities of patients with SLOS.

In summary, we present a series of 20 anesthetics administered to 14 patients with SLOS. In our series, although patients with SLOS can have difficult intubations, mask airway was always adequate, and fiberoptic intubation of the trachea was a safe and reliable option as an initial technique in airway management. Despite a history of gastroesophageal reflux disease predominantly associated with feedings, we saw no cases of aspiration of gastric contents. Our findings suggest that although SLOS patients can present with a broad spectrum of phenotypes and congenital abnormalities that are potentially challenging for the anesthesiologist, they usually require rather routine anesthetic management.

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Severe Rhabdomyolysis after Laparoscopic Surgery for Adenocarcinoma of the Rectum in Two Patients Treated with Statins

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RHABDOMYOLYSIS is a clinical and biochemical syndrome resulting from skeletal muscle injury with the release of muscle contents into the plasma. It results either from a direct muscle injury or from an altered metabolic relationship between energy production and consumption in muscle. Crush syndrome, extensive burns, electric shock, and prolonged immobilization are the main causes of direct muscle injury. Strenuous physical exercise, malignant hyperthermia, muscle ischemia resulting from compression or vascular injury, infections, myopathies, toxins, and drugs, including alcohol, which accounts for 20% of the cases, can cause nontraumatic rhabdomyolysis. This syndrome has been described with fibrates and statin lipid-lowering drugs, culminating in the recent removal of cerivastatin from the market because of a number of rhabdomyolysis-related deaths.¹ Severe cases were reported in elderly patients and in patients taking lipid-lowering drugs. We observed two consecutive cases of severe postoperative rhabdomyolysis in patients who underwent elective laparoscopic surgery for adenocarcinoma of the rectum, and for whom cumulative risk factors were identified in retrospect: long-term treatment with statins and laparoscopic surgery with prolonged immobilization under general anesthesia.

Case Reports

Case 1

A 52-yr-old male patient (body mass index, 26.6) was scheduled to undergo elective surgery for adenocarcinoma of the rectum. He had a history of myocardial infarction, moderate hypertension, pulmonary embolism, appendectomy, hypercholesterolemia, and diabetes mellitus. His usual medications included aspirin, foscipril, atenolol,

glimepiride, and pravastatin, which were discontinued the day before surgery. Preoperative evaluation of the patient did not show any biologic disturbances, and his chest radiograph was normal. The patient was premedicated with 50 mg hydroxyzine the evening before the surgery and 100 mg hydroxyzine 2 h before his admission to the operating room. Antibiotic prophylaxis (cefotaxime, 2 g) was given intravenously before the induction of anesthesia with propofol (3 mg/kg), sufentanil (0.5 µg/kg), and cisatracurium (0.15 mg/kg) for muscle relaxation. Anesthesia was maintained with isoflurane in an oxygen-air mixture supplemented with sufentanil (1.8 µg · kg⁻¹ · h⁻¹) and additional doses of cisatracurium as needed. The support points were protected by gelatin patches and checked at each change of position. The rectotomy lasted 6 h in a lithotomy position. The patient's systolic blood pressure remained above 80 mmHg during the surgery, and his perioperative blood loss was less than 500 ml. Volume replacement was ensured by administering 500 ml of a hydroxyethyl starch solution (200,000/0.5/6%/5) and 4,300 ml of crystalloids. The patient was extubated 1 h after arrival in the intensive care unit. On the first day after the surgery, the patient complained about his calves despite intravenous morphine (patient-controlled analgesia). No compartment syndrome sign was observed, and his abdomen was soft. The serum creatine phosphokinase (CPK) concentration was 7,103 IU/ml (fig. 1). On the second day, the patient's temperature increased (38°C), blood gases showed metabolic acidosis, his serum lactate concentration was 4.75 mM, and a chest radiograph revealed mixed alveolar-interstitial infiltrates. Ventilatory assistance was required as a result of acute respiratory failure. A laparotomy failed to show a surgical complication. On the third day after the surgery, the patient developed oliguric acute renal failure with a serum creatinine concentration of 272 µM and a creatinine clearance of 26 ml/min (fig. 1). Laboratory investigations revealed that his CPK concentration was 2,191 IU/l, his aspartate aminotransferase concentration was 234 IU/l, and his serum myoglobin concentration was 1.98 ng/ml. Continuous venovenous hemofiltration was initiated, and the patient's renal and respiratory function recovered slowly, as did the clinical sign of rhabdomyolysis. Serum CPK reached the maximum concentration 10 days after admission to the intensive care unit and returned to normal values 4 days later. The patient left the intensive care unit 30 days after his admission without apparent sequelae.

Case 2

A 63-yr-old male patient (body mass index, 32.8) was scheduled for the same surgery. His medical history revealed that he had undergone cardiac surgery (coronary artery bypass grafting) and an appendectomy, and that he had glaucoma and hypercholesterolemia. His usual medications included diltiazem, losartan, a potassium-sparing diuretic (furosemide-amiloride), acenocoumarol (discontinued 5 days before surgery), and fluvastatin (discontinued the day before surgery). Electrocardiogram, chest radiograph, complete blood count, coagulation

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