Anesthesia concerns for children with tuberous sclerosis

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Tuberous sclerosis (TS) is a relatively rare, autosomal dominant syndrome that displays high genetic penetrance in affected families. It is identified by a classic triad of symptoms including epilepsy, skin lesions, and mental retardation. Tuberous sclerosis causes hamartomas in multiple organ systems, including the brain, skin, heart, kidneys, lungs, and liver. Awareness of the signs and symptoms and the organs involved is critical to provide safe and effective anesthesia care.

We describe a 10-year-old girl with TS scheduled to receive a general anesthetic for laser treatment of facial angiofibromas. The patient had several coexisting maladies from TS, including hypertension, autism, seizure disorder, cardiac rhabdomyomas, developmental delay, and bilateral polycystic renal disease.

The laser procedure was performed, and there were no surgical or anesthetic complications. However, the potential for complications due to TS remained high throughout the provision of anesthesia care. Increased knowledge of TS and diligence in anesthesia practice can greatly reduce these risks.

Key words: **Anesthesia, Bourneville, children, tuberous sclerosis.**

Many anesthetists misunderstand or underestimate the importance of dermatologic conditions manifested by certain diseases. Often a request for anesthesia service in a dermatology clinic is considered less important than an anesthetic in the main operating room. The attitude that some procedures are easier or less important could place patients at greater risk for complications or even death. Every anesthetic, regardless of the procedure, must be treated with the same level of vigilance and preparation. Laser treatment of a facial lesion for a child with tuberous sclerosis (TS) is an excellent example of how a lack of knowledge or inadequate preparation for a routine procedure could lead to a significant mistake.

Case summary

A 10-year-old girl with TS was scheduled to have general anesthesia for pulsed dye laser treatment of facial angiofibromas (FAs). General anesthesia was required because of the patient's history of severe mental retardation, autism, and combative behavior.

The patient was 138 cm tall, weighed 28 kg, had a blood pressure of 137/76 mm Hg, a pulse rate of 137 beats per minute, and a tympanic temperature of 36.8°C (98.2°F). Cardiac examination revealed a regular rate and rhythm with normal S1 and S2 and no murmur, rub, click, or gallop. Although the electrocardiogram was normal, her echocardiogram revealed 3 intracardiac tumors identified as possible rhabdomyomas. These tumors were located in the posterior lateral papillary muscle, the interventricular septum, and the right ventricular wall. No obstruction to blood flow was noted. All extremities showed brisk capillary refill and 2+ pulses. Coexisting diagnoses included hypertension, autism, seizure disorder, cardiac rhabdomyomas, developmental delay with a mental age of 5 years, and bilateral polycystic renal disease. There were no other physiologic abnormalities identified. Current medications included topiramate (Topamax), felbamate (Felbatol), captopril (Capoten), diphenhydramine (Benadryl), triamcinolone acetonide (Nasacort), and sulfamethoxazole and trimethoprim (Bactrim).

After baseline vital signs were assessed, the patient was premedicated with 5 mg of oral midazolam 20 minutes before the procedure. To help further reduce anxiety, the patient's mother assisted with medication administration and placement of standard monitors. Fifteen minutes after premedication, a 20-gauge intravenous (IV) catheter was placed in the left hand. The mother held the patient during inhalation induction with oxygen, nitrous oxide, and sevoflurane.

When the anesthetic depth was sufficient, a 2.5 laryngeal mask airway was placed and inflated. Inhaled anesthesia was maintained with 1.5% sevoflurane, 60% nitrous oxide, and 40% oxygen while the dermatologist performed the pulsed dye laser procedure. Before emergence, a 650-mg acetaminophen

suppository was inserted. The inhaled anesthetics were terminated, and 100% oxygen was given during emergence. When the laryngeal mask airway was removed, the oral cavity was suctioned and supplemental oxygen was administered by mask. The patient was transported to the postanesthesia care unit, reunited with her mother, and monitored until discharge in accordance with established institutional protocol. There were no reported complications during hospitalization or following hospital discharge.

Discussion

Tuberous sclerosis is an inherited autosomal dominant syndrome with high genetic penetrance that has an increased tendency to be passed to the next generation.[1,2] Tuberous sclerosis is identified by a classic triad of symptoms, including epilepsy, skin lesions, and mental retardation.[1,3] It also causes hamartomas in multiple organ systems, including the brain, skin, heart, kidneys, lungs, and liver.[4-6] Hamartomas are benign lesions of normal organ tissue that becomes highly unorganized due to a genetic mutation.[5,7,8]

History of TS

One of the first symptoms of TS was noted in 1835 by Rayer, who described the erythematous facial papules that later were termed *adenoma sebaceum*.[9,10] Cardiac tumors associated with TS were described by the German pathologist Von Recklinghausen in 1862.[1,10,11] Bourneville, a French neurologist, labeled the syndrome *sclerose tubereuse* in 1880.[1,9] This term was selected due to the superficial resemblance of the sclerotic lesions to a potato or tuber.[6,9]

In 1890, the British dermatologist Pringle described congenital skin lesions of affected patients and termed them *adenoma sebaceum*.[9,11,12] In 1908, Vogt, a German neurologist, defined the 3 definite symptoms of the syndrome as intractable epilepsy, mental retardation, and skin lesions, which has become recognized as the classic Vogt Triad of TS.[6,10,13] In 1911, Sherlock attempted to rename this clinical triad Epiloia, although the term never gained wide acceptance.[9] Tuberous sclerosis is now referred to as *tuberous sclerosis complex*, emphasizing the variance of the clinical symptoms.[1,9]

Genetics and incidence

Tuberous sclerosis is a genetic disorder that results from the loss of heterozygosity of 2 separate tumor suppressor genes.[5,7,8] The 2 genes that potentially can become altered are *TSC1* and *TSC2*.[7,8,14] TSC1 is located on chromosome 9q34.3 and usually encodes for the protein hamartin.[14] *TSC2* is found on chromosome 16p13.3 and encodes for tuberin.[14] If either gene mutates, tumors can develop in the brain, skin, heart, kidneys, lungs, or liver.[5,15] Hamartin and tuberin in combination form a tumor suppressor heterodimer complex that decreases cell proliferation.[7] In TS, these suppressor proteins cease to function, resulting in uncontrolled cell growth and tumor development.[7]

Tuberous sclerosis occurs in approximately 1:6,000 to 1:10,000 live births and usually is diagnosed during the first decade of life.[1,4] No predilection for race or sex has been identified.[4] There is a large variation in the severity of the disease.[4,6] People with mild cases can have a normal life expectancy, whereas children with severe forms of TS might die in early childhood.[2] Death occurs in approximately 75% of people diagnosed with TS by 25 years of age.[16,17] Although TS is considered an inherited disease, approximately 60% of new cases are due to spontaneous mutations.[18]

Systemic manifestations of TS can include seizures, mental retardation, FAs, ash leaf spots, giant cell astrocytomas (GCAs), angiomyolipomas (AMLs) of the kidney, rhabdomyomas, adenoma of the liver, skeletal cysts, and lymphangioleiomyomatosis in the lungs[4,6] (Table). Skeletal muscle, peripheral nerves, and the spinal cord are the only tissues unaffected by TS tumor growth.[2,6,18]

Table. Major and minor clinical features used to diagnose tuberous sclerosis

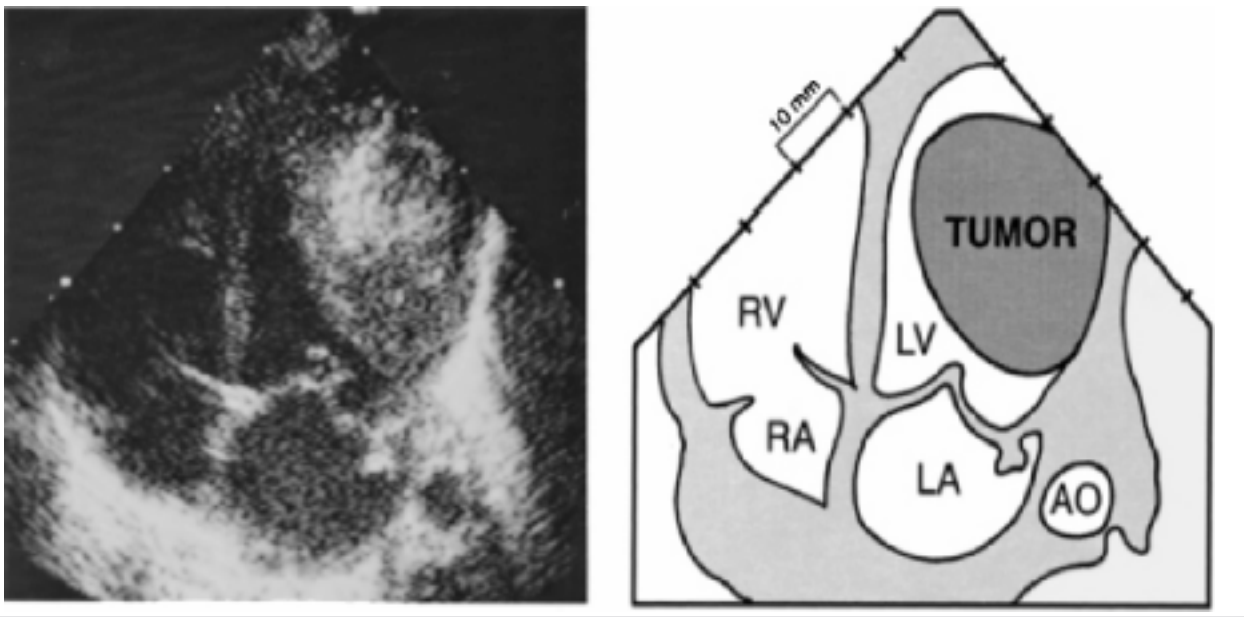
Major	Minor
Seizure disorder	Dental pits
Mental retardation	Gingival fibromas
Facial angiofibromas	Hamartomatous rectal polyps
Periungual fibroma	Autism
Ash leaf spots (>3)	Bone cysts
Shagreen patch	Liver hamartomas
Renal hamartomas	Cerebral white matter migration lines
Cortical tuber	Nonrenal hamartomas
Subependymal nodule	Retinal achromatic patch
Giant cell astrocytoma	Confetti skin lesions
Cardiac rhabdomyoma	Renal cysts
Lymphangiomyomatosis	
Renal angiomyolipoma	

(Adapted from Dinno ND. *Griffith's 5-Minute Clinical Consult.* 10th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2002:1124-1125, and Roach ES, Gomez MR, Northrup H. Tuberous sclerosis complex consensus conference: revised clinical diagnostic criteria. *J Child Neurol.* 1998;13:624-628.)

Pathophysiology of TS

- *Heart.* Rhabdomyomas are tumors that arise from

Figure 1. Rhabdomyoma in the left ventricle shown on echocardiogram



RV indicates right ventricle; RA, right atrium; LV, left ventricle; LA, left atrium; and AO, aorta.

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the myocardium in approximately 60% of patients with TS who are younger than 18 years[19,20] (Figure 1). Of the tumors, 40% are discovered during the first year of life.[20] Although rhabdomyomas are benign neoplasms that arise from muscle tissue, they result in problems related to their location and size and ultimately lead to ventricular hypertrophy, heart failure, and sudden death.[19,20] Larger rhabdomyomas may decrease or obstruct blood flow within the heart, and intracavitary tumors often mimic the symptoms of valvular stenosis.[19,21] Rhabdomyomas located in proximity to heart valves commonly cause murmurs and regurgitation.[19] The turbulent blood flow caused by these tumors increases the potential for thrombus development and the likelihood of myocardial infarction or stroke.[20]

When located in or near conduction tissue, even benign tumors have the potential to cause arrhythmias.[19] Ventricular tachycardia is most common, but supraventricular tachycardia also is observed frequently.[6,22] In some patients, rhabdomyomas have been identified as the primary cause of Wolff-Parkinson-White syndrome.[6,22] Some tumors penetrate the epicardium and result in fluid collection in the pericardial sac.[19] The resulting pericardial effusion can lead to pericarditis and cardiac tamponade.[20]

• *Kidney.* Renal lesions, including benign or malignant AMLs, renal cysts, oncocytomas, and renal cell carcinoma, are present in approximately 80% of patients with TS.[1,6,23] Any one of theses lesions can cause hypertension, renal insufficiency, or renal failure.[6]

Angiomyolipomas are the most widespread renal lesion associated with TS and affect roughly 50% to 80% of patients with TS.[24] This tumor, a combination of vascular tissue, smooth muscle, and fat, is slow growing but multiplies rapidly and often is asymptomatic until it is larger than 4 cm.[23,25,26] When larger than 4 cm, AMLs bleed easily and can be very painful.[26,27] The incidence of AMLs increases with the patient's age.[26] Patients with TS and AMLs also have an increased risk of developing malignant kidney tumors.[24]

The second most prevalent kidney problem associated with TS is bilateral renal cysts.[26] Cysts generally appear before the age of 3 years and can collapse, making radiologic detection difficult.[26] Due to the expanding renal cyst pressing on the surrounding parenchyma, hypertension is the most common related symptom.[26,28]

Oncocytomas and renal cell carcinoma affect only about 2% of patients with TS.[6,28] If these highly metastatic tumors occur, they tend to be multicentric and bilateral, typically occurring during the second decade of life.[6,28]

• *Liver.* Although they are rare, AMLs in the liver can result from TS.[29] More than half of all hepatic AMLs are associated with TS.[29] Although the symp-

toms, pain and bleeding, are similar to a renal AML, hepatic AMLs do not tend to multiply and usually are found as a single tumor in the right lobe.[30] Hepatic AMLs are slow growing and usually asymptomatic but can become larger than 15 cm and may rupture resulting in hemorrhage.[30] They often are misdiagnosed as hepatocellular carcinoma due to their similarity in clinical manifestations.[29,30]

• *Lungs.* Two pulmonary conditions generally associated with TS are lymphangioleiomyomatosis and multifocal micronodular pneumocyte hyperplasia (MMPH).[31-33] Both primarily affect women between the ages of 20 and 40 years.[1,33,34] Lymphangioleiomyomatosis causes interstitial smooth muscle proliferation that leads to interstitial thickening, alveolar damage, and, finally, chronic fibrosis of the lung.[27,34] In MMPH, multiple nodules are formed from alveolar septa, and type II pneumocytes proliferate.[27,34] Symptoms of lymphangioleiomyomatosis and MMPH include increasing dyspnea, hemoptysis, recurring pneumothorax, pulmonary hypertension, and, eventually, cor pulmonale.[1,27,33,34] Spirometry in lymphangioleiomyomatosis demonstrates an obstructive or combined obstructive-restrictive ventilatory pattern.[16]

• *Central nervous system.* Neurologic manifestations of TS are the leading cause of morbidity and mortality before the age of 30 years.[6] The 3 brain lesions most common in TS are subependymal nodules, cortical tubers, and GCAs.[6] These 3 neoplasms are believed to cause mental retardation, autism, hyperactivity disorder, and seizures.[35,36]

Subependymal nodules are the most frequently occurring brain tumor in patients with TS.[3] These neoplasms emerge near the outer edge of the lateral ventricles and tend to gather calcium during the first few years of life.[35] This increased calcium permits easier tumor detection by computed tomography scan.[1,35] The nodules are not directly responsible for neurologic problems but may increase pressure on surrounding tissues and decrease brain function by the mass effect.[35]

Cortical tumors usually are found shortly after birth in patients with TS.[6] They generally occur in small areas of the cortex that are not properly developed and alter the structure of the brain and, therefore, its function.[6] Cortical tumors are thought to be the cause of the intractable seizures commonly found in patients with TS.[6]

Giant cell astrocytomas are benign tumors that develop in approximately 15% of people with TS.[1,35] Typically, they appear in older children, and occurrence decreases after adolescence.[24] Although GCAs have many histological similarities to subependymal nodules, GCAs tend to be larger with more aggressive growth.[1] They often form near the foramen of Monroe and cause a reduction in the flow of cerebrospinal fluid from the lateral to the third ventricle.[3,37] A GCA may cause obstructive hydrocephalus, increased intracranial pressure, and a heightened potential for cerebral infarct or aneurysm[2,3] (Figure 2).

Seizures associated with TS are one of the first and most common signs of the disease.[38] Seizures affect approximately 84% to 96% of patients with TS.[5,38,39] Epilepsy in TS tends to be uncontrolled by most medications.[40] Two medications that have shown promise are lamotrigine (Lamictal) and vigabatrin (Sabril).[41] Lamotrigine acts to block sodium channels, thereby decreasing the release of neurotransmitters.[41] Vigabatrin acts to irreversibly block gamma-aminobutyric acid transaminase and is particularly effective for infants.[41] In TS, nearly 90% of drug-resistant intractable epileptic seizures are reduced with surgical resection of the focal seizure tissue.[38,40]

• *Skin.* Facial angiofibromas, originally termed *adenoma sebaceum*, are the most common lesion, occurring in 80% to 90% of patients with TS.[4,9,17,42] They are usually small, erythematous papules distributed in a butterfly pattern around the nose[3,4,43] (Figure 3). These papules generally increase in size with age.[3,43] By comparison, FAs may seem insignificant, but they are one of the principal reasons people seek treatment.[44] The FAs may become large and cause significant facial alteration, resulting in emotional, vision, and airway problems.[44]

There are other dermatologic abnormalities noted in TS. Ash leaf spots are found on the thoracoabdominal area of more then 90% of patients with TS and often are the first dermatologic signs of the disease.[3] Ash leaf spots are oval, hypopigmented macules that commonly are found at birth and best detected with an ultraviolet (Wood) lamp.[1,4,17,42] Shagreen patches, most commonly found in the lumbosacral region, are soft, tan or yellow plaques with a rough texture much like that of an orange peel or of pigskin.[17,42] Periungual fibromas are present in about 20% to 50% of patients with TS.[4] They usually are found during puberty.[4] These tumors are smooth, flesh-colored, protrusions from the nailbed of the patient's fingers or toes.[42] Skin hamartomas occur more often than any other clinical sign in TS.[3]

Anesthetic considerations

Having the parents present during the preoperative examination and interview is essential to achieve a successful anesthetic experience for the child and par-

Figure 2. Coronal magnetic resonance image showing a giant cell astrocytoma invading the lateral ventricle

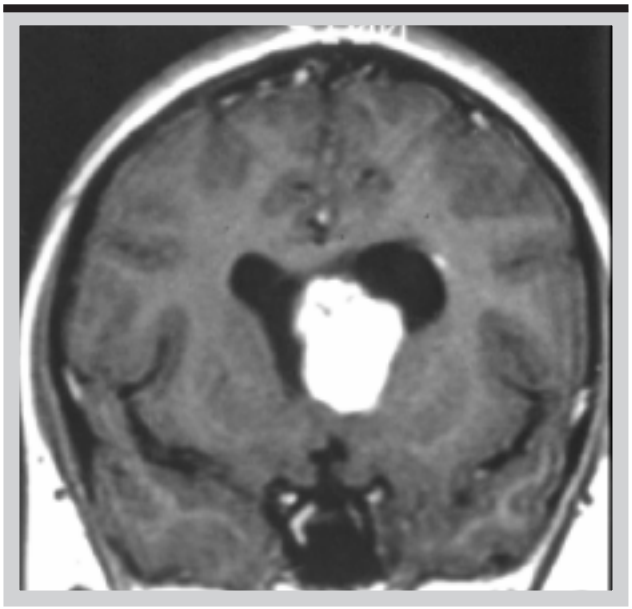

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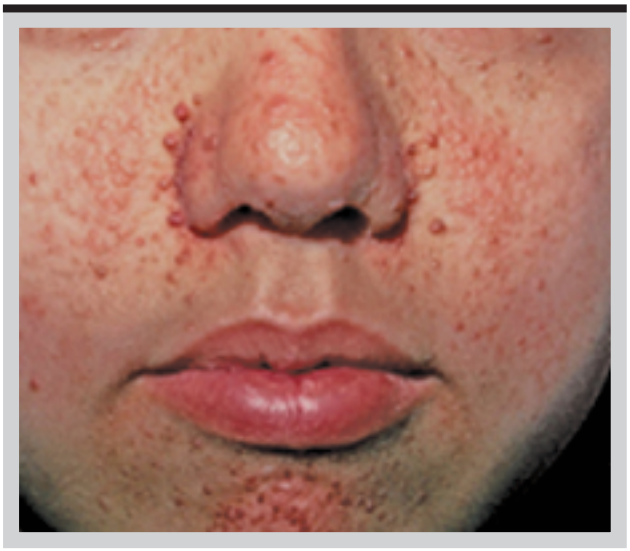
Figure 3. Facial angiofibromas



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ents.[45] The anesthetist must gain the patient's and the parent's trust during this period to decrease the anxiety of separation from their child.[45] If there have been prior anesthetics, this is an opportune time to ask the parents what methods were previously successful with their child.[45]

Allowing parents to assist with simple tasks before induction, such as monitor placement or premedication, can be helpful in relieving parental stress.[45,46] This parental involvement can add familiarity for the patient. Studies have shown a decrease in the anxiety level of the child and the parents when the parents assist with the care.[45-47]

A complete history and physical examination are imperative because organs affected by TS can vary greatly from one patient to the next. Before general anesthesia, it is recommended that a patient with TS have the following tests: chest radiographs, electrocardiogram, transthoracic echocardiogram, anticonvulsant medication levels, electrolytes, blood urea nitrogen, and creatinine.[13]

Premedication is advantageous because many patients with TS have behavior problems.[21,36,45,47] Barbiturates may enhance seizure suppression and decrease cerebral metabolic rate while maintaining blood flow to the brain.[13] Rectal methohexital, 20 to 30 mg/kg, may be used and, in most patients, provides sedation within 10 minutes.[45] Methohexital has been associated with seizure activity and is contraindicated in children with epilepsy.[45] Benzodiazepines are useful because they also aid in suppressing seizure activity, but unlike barbiturates, are reversible with flumazenil if respirations become depressed.[13] Midazolam can be given IV, 0.02 to 0.05 mg/kg; intramuscularly, 0.1 to 0.15 mg/kg; orally, 0.25 to 0.5 mg/kg; or rectally, 0.3 to 0.75 mg/kg.[45] Short-acting medications like methohexital or reversible medications such as midazolam are considered optimal for decreasing postoperative complications.[45] An oral midazolam dose of 0.25 to 0.5 mg/kg has been shown to provide peaceful separation and amnestic effects after 10 minutes, and anxiolysis occurs within 15 minutes.[48] Ketamine should be avoided in patients with TS because it lowers the seizure threshold and increases intracranial pressure.[13]

Placement of an IV catheter can be delayed until after the anxiolytic has taken effect.[21,45] The IV catheter must be placed before induction due to the elevated risk of complications with TS, such as cardiac arrhythmias and seizures.[49] Propofol, 2.5 to 3.0 mg/kg, can be used for induction if the patient is free of cardiac involvement.[13,45] If cardiac pathology is significant, etomidate, 0.3 mg/kg, is the drug of choice.[13,45] Alternatively, sevoflurane and nitrous oxide can be used by mask for inhalation induction.[45]

Anesthesia can be maintained with sevoflurane, desflurane, or isoflurane in oxygen and nitrous oxide or air.[13] A minimum fraction of inspired oxygen of 0.4 should be maintained due to the likelihood of cardiopulmonary pathology.[13] This will ensure adequate oxygen availability for the myocardium and help dimin-

ish arrhythmias induced by ischemia.[50] If cardiac function is not compromised, propofol can be titrated to effect as a continuous infusion.[45] Some possible advantages of a propofol infusion include decreased laryngospasm, decreased nausea, and earlier emergence.[45]

Analgesia can be well controlled with IV fentanyl, 1 to 2 µg/kg.[50] This medication is an excellent selection because it is easily metabolized by the liver, has limited cardiovascular effects, and is rapidly eliminated in children older than 3 months.[45,50] Due to duration of action and active metabolites, morphine and meperidine are best avoided, especially if renal function is impaired.[50] Caution is warranted in spontaneously breathing patients, opioids can decrease respiratory rate with resulting hypercarbia, potentially raising intracranial pressure and increasing seizures.[13]

Renal and hepatic function of patients with TS can affect the selection of a neuromuscular blocker. If the patient has decreased liver function, rocuronium may be a better choice than vecuronium because vecuronium is primarily metabolized by the liver.[45,49] The elimination of rocuronium and vecuronium can be prolonged if renal function is compromised.[45,49] Mivacurium, atracurium, and cisatracurium may be the safest choices in renal or liver failure due to their absence of hepatic metabolism, inactive metabolites, and low percentage of renal clearance.[13,45,49]

Postoperatively, patients with TS should be monitored closely for seizure activity.[13] High or low carbon dioxide levels may increase the potential for a seizure.[13] To avoid inappropriate levels of carbon dioxide, keep the patient euvolemic and normocarbic and provide adequate pain relief.[13] Control of tachypnea and preservation of a normal respiration rate decrease seizure potential.[13]

Conclusion

Perioperative management of patients with TS often is complicated by the presence of cardiovascular, neurologic, and renal tumors.[21] Tuberous sclerosis affects many organ systems, and the anesthetist must be ready to meet these challenges. Careful attention must be given to the preoperative evaluation to discern the involvement of each system and the extent and severity of the disease process. A thorough assessment of the individual is crucial for developing a safe anesthetic plan for all patients, including those with TS.

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