Trisomy 21 and Anesthesia

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Trisomy 21 (Down syndrome): most common congenital abnormality in United States (6.3 per 10,000 live births); occurs across ethnicities; ≈500,000 children in North America affected; incidence increases with increasing maternal age; also caused by balanced or unbalanced translocation of chromosome 21 or mosaicism (phenotypes indistinguishable); diagnosis possible during pregnancy through chorionic villus sampling or amniocentesis with karyotyping

Physical abnormalities: smaller-than-normal size for age, short neck, microbrachycephaly, oblique palpebral fissures, epicanthal folds, small low-set ears, enlarged tongue, microdontia, and fused teeth, mandibular hypoplasia, and broad flat nose; challenges in intubation numerous

Respiratory system: respiratory tract infections common; anatomy abnormal; incidence of postoperative obstruction of airway high; ability to handle secretions poor; speaker recommends postponement of elective procedures for patients with upper respiratory tract infection; immune deficiency often present; incidence of sleep apnea high; risk for desaturation high; speaker considers children with Down syndrome inappropriate candidates for outpatient tonsillectomy

Airway: subglottic stenosis often present (use endotracheal [ET] tube 1 or 2 sizes smaller than normal); ensure presence of leak around cuffed ET tube to minimize risk for croup; postextubation stridor occurs in 30% to 40% of children with Down syndrome compared with 2% of chromosomally normal children; hypoventilation frequently occurs with sedation; risk for respiratory depression and obstruction high; consider possible pulmonary hypertension; monitor appropriately during and after procedure

Cardiovascular system: incidence of disease high; endocardial cushion defects present in 40%; ventricular septal defects (VSDs), 27%; patent ductus arteriosus (PDA), 12%; tetralogy of Fallot, 8%; other cardiovascular anomalies, 13%; abnormalities often remain after correction

Pulmonary hypertension: develops earlier regardless of presence or absence of cardiac disease; possible causes elevated levels of carbon dioxide or underlying cardiac disease; resuscitation after cardiac arrest difficult

Atropine: earlier studies recommend avoidance of use because of perception of high sensitivity; recent studies suggest atropine indicated because of low sympathetic nervous system activity and high level of secretions

Prophylactic antibiotics: use indicated in children who have undergone heart surgery (except repair of simple atrial septal defect, VSD, or PDA) or have complex congenital heart disease (particularly before tonsillectomy and neurologic procedures)

Immune system: relative immune deficiency present; sterile technique required for insertion of invasive lines; incidence of positive results for hepatitis B surface antigen test high; incidence of polycythemia higher than normal in neonatal period; incidence of acute lymphocytic and myeloblastic leukemia in older children with Down syndrome 20 times higher than in chromosomally normal children

Endocrine system: incidence of hypothyroidism (congenital or adult onset) high; hypothyroidism frequently undiagnosed (presents challenges in anesthesia); blood pressure lower than normal; lower levels of catecholamines in blood may decrease minimum alveolar concentration (MAC) of anesthetic agents; sensitivity to sedatives and anesthetic agents higher (titrate to desired effect)

Gastrointestinal system: incidence of duodenal atresia, Hirschsprung disease, and gastroesophageal reflux high

Central nervous system: intellectual disability universally present; incidence of anxiety on separation from caregivers high; muscle hypotonia contributes to postoperative obstruction of airway; incidence of strabismus higher than normal; exaggerated response to nondepolarizing muscle relaxants present in 75% (careful titration and use of reversal agents necessary); epilepsy present in 10% (continue medications on day of surgery, because intravenous form of many medications unavailable)

Ophthalmologic procedures: performed to manage cataracts, hypermetropia, astigmatism, strabismus, glaucoma, keratoconus, obstruction of nasolacrimal duct, and nystagmus; examination of eyes during neonatal period important; during examination, maintain head and neck in neutral position and avoid forcible rotation of neck

Atlantoaxial instability: affects 10% to 20% of individuals with Down syndrome; prevalence higher in children than adults; atlantoaxial distance measured between odontoid process and anterior arch of atlas during radiography of lateral cervical spine.

Educational Objectives

The goal of this program is to improve the anesthetic treatment of children with Down syndrome and the quality of sedation using dexmedetomidine. After hearing and assimilating this program, the clinician will be better able to:

1. Identify the physical and physiologic characteristics of children with Down syndrome that affect the delivery of anesthesia and sedation.
2. Implement perioperative protocols and techniques that accommodate the requirements of children with Down syndrome.
3. Explain the mechanism of action and pharmacokinetics of dexmedetomidine.
4. Administer appropriate dosages of dexmedetomidine.
5. Evaluate recent studies on the efficacy of dexmedetomidine.

Faculty Disclosure

In adherence to ACCME Standards for Commercial Support, Audio Digest requires all faculty and members of the planning committee to disclose relevant financial relationships within the past 12 months that might create any personal conflicts of interest. Any identified conflicts were resolved to ensure that this educational activity promotes quality in health care and not a proprietary business or commercial interest. For this program, members of the faculty and planning committee reported nothing to disclose. In his lecture, Dr. Lerman presents information related to the off-label or investigational use of a therapy, product, or device.
cervical spine; normal distance 4 to 5 mm; patients symptomatic at 5 to 6 mm; neurologic manifestations at ≥7 mm; subluxation may cause spinal cord compression; symptoms include weakness in extremities and preference for sitting; obtain history of physical activity and report on recent radiograph of cervical spine

Physical signs: abnormal gait, preference for sitting, hyperreflexia, clonus, neurogenic bladder, hemiparesis, ataxia, and sensory loss; symptoms occur in patients with atlantoaxial instability (eg, during movements of head)

Recommendations of Committee on Sports Medicine of American Academy of Pediatrics: all children with trisomy 21 should undergo radiography of cervical spine before participation in sports; large atlantoaxial interval or bony abnormality of first or second cervical vertebra criteria for exclusion; required interval for repeating radiography undefined

Current recommendations: perform thorough history and physical examination preoperatively; no further workup necessary if patient asymptomatic; in administration of general anesthesia, avoid unnecessary head movements, forced flexion, excessive rotary motion, and extension (flexion and rotary motion compress spinal cord); maintain neutral position; review radiograph of cervical spine; consider neuromuscular consultation if atlantoaxial distance ≥4.5 mm; preoperative radiography and neuromuscular consultation mandatory if neurologic signs or symptoms present; consider changes since radiography performed; at least one baseline radiograph recommended

Anesthetic challenges: vascular access often difficult; evaluate patient for cardiac disease; consider prophylaxis for subacute bacterial endocarditis; potential for subglottic stenosis high (select ET tube accordingly); avoid outpatient tonsillectomy; take precautions if atlantoaxial instability present

Management: monitor patient who has received premedication; administer intramuscular ketamine or oral ketamine 3 mg/kg with midazolam 0.5 mg/kg for premedication; encourage presence of primary caregiver during induction of anesthetic agent; prepare to treat airway obstruction and bradycardia; junctional rhythm may occur with use of sevoflurane; vagal blockade may cause profound tachycardia (administer atropine, if indicated); use ET tube smaller than normal for age; maintain neutral neck position; use sterile technique for insertion of catheters; monitor patient for sleep apnea and stridor during postoperative period

Suggested Readings

Dexmedetomidine in Pediatric Patients
Jerrold Lerman, MD, Clinical Professor of Anesthesiology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, The State University of New York, and Women and Children’s Hospital of Buffalo, NY

Characteristics: primarily used in Europe for adults in intensive care unit (ICU); use in children or anesthesia underdeveloped; patent expired in 2015; mechanism of action — α2 adrenergic receptor in brain triggered; primary action by way of locus caeruleus; in animal studies, apoptosis not triggered; effects associated with α2A and α2B adrenergic receptors varied; adverse effects — bradycardia or tachycardia, and hypertension or hypotension (effect varies with method of administration); decrease in shivering; diuresis

Effects: sedation and analgesia (not general anesthesia); minimum alveolar concentration (MAC) of anesthetics reduced by 30% (maximum); effects on respiratory rate and tidal volume limited; airway obstruction improved or relieved; blood pressure controlled; oxygen demand decreased; stimulation prevented

Medetomidine: parent drug of dexmedetomidine; use in veterinary medicine extensive

Comparison of dexmedetomidine with clonidine: specificity for α2 adrenergic receptor 8 times greater; peripheral effects fewer

Sedation: role in pediatric patients not well defined; drug used for sedation in various procedures and by range of health care providers; by nurses in some jurisdictions as single agent for sedation; in operating room as sedative during total intravenous (IV) anesthesia, for patients with unstable cervical spines, and for management of airway; for premedication; and in ICU

Pharmacokinetics: onset of sedation slow (effects develop 10 min after administration of loading dose); elimination half-life 2 hr at dose of 1 μg/kg (drug administered as constant infusion over long period accumulates); agent lipophilic; children semi-conscious during elimination period

Route of administration: buccal — bioavailability ≈80%; peak blood levels achieved in 90 min; oral — bioavailability 16%; intramuscular — bioavailability 100%; using any route of administration, peak blood levels achieved in 1.5 to 2 hr (limits suitability for ambulatory surgery)

Clearance: ≈50% of adult levels in young children; 85% of adult levels at age <1 yr; drug action particularly long for patients in neonatal ICU and young babies; infusion calculated as micrograms per kilogram per hour (micrograms per kilogram per minute for other drugs); after 1-hr infusion, 50% reduction in blood concentration requires ≈75 min; 80% reduction, 4 hr; drug highly protein bound and extensively metabolized; elimination half-life markedly higher for patients with hepatic failure or insufficiency; elimination primarily by conjugation and elimination

Use in pediatric ICU: incomplete anesthetic (suitable for sedation); airway maintenance; provision of analgesia; literature inconclusive (more studies of efficacy needed)

Obesity: dexmedetomidine lipophilic; Cortinez et al (2015) found plasma concentrations ≈50% higher in obese patients (BMI ≥35) compared with lean (BMI <30); further evaluation of models required to determine of predictable blood levels during infusion (use of lean body mass to calculate dosage optimal)

Premedication: onset of action slow (1 hr for intranasal and buccal administration; slower than for oral midazolam); Yuen et al (2010) found 25-min onset in ≥50% of children for 1 μg/kg administered intranasally; Mahmoud et al (2010) found oxidative metabolism of models required to determine of predictable blood levels during infusion (use of lean body mass to calculate dosage optimal)

Airway: respiration preserved; Mahmoud et al (2010) found dexmedetomidine beneficial for respiration; Mahmoud et al (2009) suggest dexmedetomidine preferable to propofol for patients with obstructive sleep apnea (OSA); beneficial effects increase with increasing severity of OSA

Cardiovascular system: hypertension, hypotension, and bradycardia may occur; rapid IV administration of 1 μg/kg causes profound transient hypertension; loading dose normally infused over 10 min; typical maintenance infusion dosages 0.2 to 1.0 μg/kg/hr; effects (particularly on heart rate) exaggerated at high dosages; higher dosages evaluated for provision of sedation by single nonphysician operator

Mason et al (2008): retrospective review of loading dose of 3 μg/kg followed by infusion of 2 μg/kg/hr for magnetic
resonance imaging (MRI) found decreased heart rates (<60 beats per minute) in children (low enough to trigger cardio-pulmonary resuscitation in babies).

Ahmed et al. (2015): evaluated loading dose of 2 μg/kg followed by infusion of 1 μg/kg/hr; found 20% of patients required additional bolus and 20% required additional medications to complete MRI; incidence of hypotension 20%; incidence of bradycardia 4%; almost all adverse effects resolved spontaneously.

**Discharge times:** Heard et al. (2008) found 15 min longer time to discharge compared with propofol; Ahmed et al. (2015) found 90 min to discharge; Mason reports achievement of discharge times of 25 to 35 min after high dosages when children’s faces rubbed with wet cloth to transiently rouse them; no cases of respiratory arrest reported; Heard et al. (2015) found discharge time for propofol and isoflurane 70 min.

**Anticholinergic medications:** cause hypertension when administered in combination with dexmedetomidine; use in treatment of bradycardia during administration of dexmedetomidine contraindicated.

**Emergence delirium:** prevented by dexmedetomidine after administration of sevoflurane and desflurane; *study of dexmedetomidine administered at end of tonsillectomy* — bispectral index 45 to 55 maintained; sevoflurane concentration decreased in dexmedetomidine arm; extubation, emergence, and discharge times faster in dexmedetomidine compared with sevoflurane arm; *study by Kim et al. (2015)* — determined 0.38 μg/kg as 95% effective dose for prevention.

**meta-analysis** — dexmedetomidine effective for prevention compared with placebo.

**Suggested Readings**


*Kim HS et al.*: Appropriately dose of dexmedetomidine for the prevention of emergence agitation after desflurane anesthesia for tonsillectomy or adenoidectomy in children: up and down sequential allocation. *BMC Anesthesiol* 2015 May 27;15:79;


*Mason et al.*: High dose dexmedetomidine as the sole sedative for pediatric MRI. *Paediatr Anaesth* 2008 May;18(5);403-11;


*Vilo S et al.*: Pharmacokinetics of intravenous dexmedetomidine in children under 11 yr of age. *Br J Anaesth* 2008 May;100(5):697-700;


**Acknowledgments**

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**Estimated time to complete the educational process:**

- Review Educational Objectives on page 1: 5 minutes
- Take pretest: 10 minutes
- Listen to audio program: 60 minutes
- Review written summary and suggested readings: 35 minutes
- Take posttest: 10 minutes
1. Which of the following physical abnormalities is characteristic of children with Down syndrome?
   (A) Larger-than-normal size for age  (C) Macrodontia
   (B) Enlarged tongue  (D) Mandibular hyperplasia

2. All the following are physiologic characteristics of children with Down syndrome that must be accommodated during anesthesia and sedation, EXCEPT:
   (A) Decreased ability to handle respiratory secretions
   (B) High risk for hyperventilation
   (C) High risk for respiratory depression and obstruction
   (D) High risk for pulmonary hypertension

3. Which of the following cardiovascular abnormalities is most prevalent in children with Down syndrome?
   (A) Endocardial cushion defect  (C) Patent ductus arteriosus
   (B) Ventricular septal defect  (D) Tetralogy of Fallot

4. In children with Down syndrome, abnormalities of the endocrine system often cause:
   (A) Hypothyroidism
   (B) Hypertension
   (C) High catecholamine levels in the blood
   (D) High minimum alveolar concentrations (MAC) of anesthetic agents

5. A patient with an atlantoaxial distance of 6 to 7 mm:
   (A) Requires special management during anesthesia
   (B) Requires no preoperative neurosurgical consultation
   (C) Manifests no neurologic abnormalities
   (D) Is considered normal

6. The elimination half-life of a 1-μg/kg dose of dexmedetomidine is:
   (A) 30 min  (B) 1 hr  (C) 2 hr  (D) 4 hr

7. Dexmedetomidine administration leads to peak blood levels in _______ using any rate of administration.
   (A) 2 to 3 min  (B) 10 to 15 min  (C) 1.5 to 2 hr  (D) 2 to 3.5 hr

8. In which of the following ways does dexmedetomidine differ from other sedatives?
   (A) Maintains the airway
   (B) Has a short half-life
   (C) Doses calculated in micrograms per kilogram per minute
   (D) Does not provide analgesia

9. According to a study by Cortinez et al (2015), how do plasma concentrations of dexmedetomidine differ in obese compared with lean patients?
   (A) ≈30% higher  (B) ≈50% higher  (C) ≈30% lower  (D) ≈50% lower

10. Adverse cardiovascular effects of dexmedetomidine include all the following, EXCEPT:
    (A) Bradycardia  (B) Cardiac arrest  (C) Hypotension  (D) Hypertension

Answers to Audio Digest Anesthesiology Volume 58, Issue 35: 1-B, 2-A, 3-C, 4-C, 5-D, 6-B, 7-D, 8-D, 9-C, 10-B