

TIVA- What is its place today?

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Inhalational anesthesia has been the mainstay of pediatric anesthesia since its "beginnings" in 1849. However, the introduction of intravenous catheters and intravenous anesthetics in the second half of the twentieth century has facilitated the development of TIVA (total intravenous anesthesia), first in adults and more recently in children. Despite the availability of the equipment for and knowledge of the pharmacology of TIVA in children, this technique has not supplanted inhalational anesthesia. Nonetheless, TIVA has carved a role in pediatric anesthesia in several specific areas: for anesthesia outside the operating room, in MH and hypotonic children, awake craniotomy, for scoliosis surgery where motor evoked potentials are required and in the intensive care unit. In this lecture, we shall review several of the considerations for TIVA in children.

To understand how TIVA can have a role in anesthesia for children, I have listed several of the salient Pros and Cons of this technique:¹

Pros: absence of operating room and environmental pollution (if N₂O is omitted), titratable depth of anesthesia, lack of sympatholysis, MH safe and the absence of emergence delirium.

Cons: IV access required, drugs cannot be readily withdrawn once administered, risk of propofol infusion syndrome, risk of pain on injection, risk of bacterial contamination, unable to assess depth of anesthesia, difficulty in assessing the probability of awareness and use of the BIS,² sympathetic nervous system intact, movement may occur without paralysis.

TIVA has been defined by purists as involving only intravenous medications, although many include nitrous oxide in the TIVA technique. The major medications used in TIVA include midazolam, propofol and an opioid. The role of dexmedetomidine in TIVA has not yet been established. Muscle relaxants may have a role in the patient who requires tracheal intubation, but in pediatrics, that is the minority of instances.

Midazolam.

I administer midazolam for amnesia in children who require TIVA. The dose of intravenous midazolam required for children far exceeds that in adults. The dose range that I use is from 0.1 to 0.2 mg/kg depending on the duration of surgery. For younger children and if nitrous oxide is avoided, I administer the larger dose of midazolam,

mostly immediately after induction of anesthesia. If surgery extends beyond 4 hours, I will administer half the original dose again.

Propofol.

In general, the dose requirements for propofol in children are greater than for adults. In the same way as the MAC for inhaled anesthetics increases with decreasing age, so too does the induction dose of propofol. However, for maintenance of anesthesia, the same holds true. Our experience was rapidly acquired while sedating children for MRI using only propofol. I usually start the infusion at 12 mg/kg/h (200 mcg/kg/min) and decrease it 20% every 15 minutes until 6 mg/kg/h. However, younger children and those who are neurologically challenged require far greater doses of propofol to remain immobile for the scans.³ The largest dose I have administered to prevent movement has been 30 mg/kg/h for a brief period before decreasing it. I do my best to avoid tapering the dose of propofol so that the child moves. If this occurs the scan must be repeated.

Programmable infusion pumps are not approved for use in children less than 16 years of age. This is an open loop device with no feedback from the patient in the form of BIS, hemodynamics or blood levels.¹ In a study of continuous infusions with propofol using the Diprifusor in children 3-11 years of age, McFarlan et al concluded that the appropriate dosing sequence to maintain a therapeutic blood concentration of 3 mcg/ml after a loading dose of 2.5 mg/kg is 15 mg/kg/h for the first 15 min, 13 mg/kg/h for the next 15, 11 mg/kg/h for the next 30 minutes, 10 mg/kg/h for the next hour and 9 mg/kg/h for hours 2 to 4.⁴ This results in a context sensitive half-lives in children that are 50% and 100% greater than those in adults respectively: 10 minutes at 1 h and 20 minutes at 4h.

Long-term propofol infusions were used extensively for sedation in intensive care after recognizing that its favorable pharmacokinetics will facilitate a rapid wake-up. However, a report of five deaths in infants and children (4 weeks to 6 years of age) who were sedated with Diprivan[®] raised serious doubts about the safety of such a practice.⁵ The syndrome, now known as PRIS (propofol infusion syndrome), occurs primarily but not exclusively in children who are sedated for prolonged periods in intensive care units.⁵⁻⁹ the most common prescription for developing PRIS is prolonged sedation at a rate of > 5-mg/kg/hour (70 mcg/kg/minute) for > 48 hours. Manifestations of PRIS include the insidious onset of lipemia, metabolic acidosis, hyperkalemia and rhabdomyolysis that may precipitously transform into profound myocardial instability and cardiovascular collapse that is refractory to all resuscitative efforts. Presenting signs may be subtle with the sudden onset of bradycardia that is refractory to the usual interventions. Of greater concern is a recent case in which a brief 6 hour infusion of propofol resulted in an unexplained metabolic acidosis in a 5 year old undergoing an arterio-venous malformation resection.¹⁰ Suspicion was raised that this may have been PRIS in evolution. Propofol was discontinued and the signs of PRIS abated. In an adult neurosurgical intensive care unit where propofol sedation was used, 5 deaths prompted a review of 12 deaths.¹¹ They determined that for every 1 mg/kg/hour that the propofol infusion exceeded 5 mg/kg/hour, the odds ratio of death was 1.93. After a total to date of at least 28 deaths in children and 14 in adults, the FDA cautioned against the use of

propofol for long-term sedation. Predisposing risk factors include concomitant catecholamine/inotrope infusions or high-dose steroids and sepsis. Mortality currently exceeds 80% although early institution of hemodialysis may improve survival. Whether these concerns ultimately cause a withdrawal of propofol during sedation for medical and surgical procedures remains to be determined.

Unraveling PRIS has proven to be difficult. Early investigations noted that during PRIS, the blood concentrations of malonylcarnitine and C5-acylcarnitine increased. These compounds are known to inhibit carnitine palmoyl transferase and the transfer of LCT into mitochondria.^{12,13} Propofol may also directly inhibit carnitine palmoyl transferase to impede flux of LCT into the mitochondria. Within the mitochondria, propofol uncouples β spiral oxidation at complex II in the respiratory chain, which in turn inhibits transmembrane flux of LCT into mitochondria, strangling the mitochondria for much needed source of energy. In order to reduce the risk of PRIS, new formulations of propofol are being developed that contain less or no LCT. MCTs are replacing LCTs in propofol.

There are no commercially available alternate lipid formulations of propofol currently on the market, although four are under investigation: SAZN 1% and 6%, Propofol-Lipopuro, IDD-D (insoluble drug delivery microdroplet) and Ampofol. SAZN 6% is formulated with MCT/LCT, has a similar pharmacology to Diprivan® but with a much reduced incidence of pain on injection. Lipopuro® is also similar in properties to Diprivan although the 2% propofol concentration produced a similar incidence of pain as Diprivan®. Propofol IDD-D (insoluble drug delivery-microdroplet) is another formulation that is based on a microdrop delivery system in which 2% propofol is combined with the 4% non-Soya MCTs without preservatives. It needs no antimicrobial protection. The pharmacology of IDD-D is similar to Diprivan and produces severe/moderate pain in less than one-third of those who received Diprivan®. One of the metabolites of this formulation, octanoate, can in theory produce neurologic complications, although the concentrations are likely sub-toxic.¹⁴ The final preparation is Ampofol which is a 1% propofol infusion in 5% soybean oil and 0.6% lecithin.¹⁵ The major detraction of Ampofol is the four-fold greater incidence of moderate pain on injection compared with Diprivan®.

Remifentanil.

This opioid has a very rapid onset and offset of action, being hydrolyzed by tissue esterases. Consequently, it must be given as a continuous intravenous infusion. Cessation of the infusion results in rapid elimination of the opioid and the acute onset of pain. Regarding its pharmacokinetics, this compound is the only compound whose clearance is more rapid in neonates than it is in older children. Indeed, the context sensitive half-life of remifentanil is approximately 8 minutes, independent of the duration of the infusion.

Remifentanil is best administered as a continuous infusion without a loading dose (to avoid chest wall rigidity and bradycardia). The infusion rates range from 0.1 to 0.25

mcg/kg/minute. Remifentanyl and propofol together have been very a effective combination for TIVA.

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