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# Paediatric total intravenous anaesthesia and target-controlled infusion

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## Introduction

Total intravenous anaesthesia (TIVA) is a technique of anaesthesia where the agents administered are given exclusively by the intravenous route, while target-controlled infusion (TCI) is a computer-controlled system that is intended to achieve a user-defined "target" drug concentration in a specific body compartment or tissue of interest.[1] It does this by performing rapid sequential calculations every 8 to 10 seconds to estimate the infusion rate required either in the plasma or at the effect site of action of the drug.[2] The use of propofol-based TIVA and TCI in the paediatric population is becoming common. There are, however, multiple considerations and limitations which do not allow for simple translation from adult data.

## Indications

The most common indications for TIVA/TCI in the paediatric population include: those at risk for malignant hyperthermia (MH) and anaesthesia-induced rhabdomyolysis (AIRS); the undiagnosed "floppy child"; those at high risk of postoperative nausea and vomiting (PONV); brief procedures where rapid recovery is required (e.g. MRI, BM aspiration, gastrointestinal endoscopy, ENT endoscopy); repeated anaesthesia (e.g. radiation therapy); neurosurgical procedures for control of intracranial pressure, cerebral metabolic protection; spinal surgery requiring evoked potential; and sedation.[3,4] Some indications are specific to the child and their comorbidities, such as emergence delirium; children presenting for surgery with concurrent upper respiratory tract infection, propofol usage is known to obtund airway reflexes and reduce airway reactivity.[5] A propofol-based TIVA should be avoided in the following circumstances: where there is a drug allergy, equipment is not available, children who have unresuscitated shock or significant cardiac dysfunction, children who may have a predisposition to propofol-related infusion syndrome (PRIS) or those known or suspected of having mitochondrial disease.[5] The advantages and disadvantages of propofol TIVA are listed in Table I and Table II.

## Pharmacokinetics and pharmacodynamics

Data on the pharmacokinetics of propofol through the paediatric age range, from neonates to the adolescent and also in the presence of comorbidities and/or critical illness, is well described.[6]

After an intravenous administration of propofol, loss of consciousness occurs 30–60 seconds after that, with the drug acting on the central nervous system. This is followed by exponential decline in three distinct phases with the drug

**Table I:** The advantages of TIVA[4,6,7]

| Factor | Benefit |
|---|---|
| Clinical | Reduced PONV<br>Reduced airway reactivity<br>Reduced laryngospasm and bronchospasm<br>Bronchodilation<br>Preserved hypoxic pulmonary vasoconstriction<br>Improved respiratory ciliary function<br>Reduced emergence delirium<br>Improved speed and quality of recovery<br>Amnesia/decreased awareness<br>Neuroprotection<br>Reduced intraocular pressure<br>Preserved middle ear pressure<br>Reduced stress hormones<br>Reduced pain |
| Anaesthetic of choice | MH susceptibility<br>Neuromuscular disease to prevent hyperpyrexia and rhabdomyolysis<br>Neurosurgical procedures<br>Scoliosis surgery with SEP and MEP monitoring<br>Middle ear surgery<br>History of severe PONV<br>Laryngotracheal bronchoscopy<br>Maintenance of spontaneous ventilation for remote location<br>Known myocardial repolarisation abnormality |
| Usability | Easily titratable<br>Sedation for transport situations<br>Sedation/anaesthesia of choice when regional technique is used<br>Reduced cost<br>Low-risk anaphylactic reaction<br>No issue with known egg or soy allergy<br>Closed loop system in development |
| Avoid complications associated with volatiles | No atmospheric pollution<br>No organo-toxicity<br>Avoid seizure potential of sevoflurane<br>Fear of masks |

PONV – postoperative nausea and vomiting, MH – malignant hyperthermia, SEP – somatosensory evoked potentials, MEP – motor-evoked potentials

**Table II:** The disadvantages of TIVA[4,6,7]

| Factor | Disadvantage |
|---|---|
| Clinical | Bacterial contamination<br>PRIS<br>Not anaesthetic of choice for some subsets of metabolic and mitochondrial myopathies<br>Potential neurotoxicity in developing brain<br>Lactic/metabolic acidosis<br>Hypertriglyceridaemia and case reports of acute pancreatitis |
| Caution due to $CST_{½}$ of propofol | Long neurological cases<br>Long neonatal cases<br>Obesity |
| Caution due to dose-dependent myocardial depression and peripheral vasodilation | Compromised cardiovascular status<br>Cardiomyopathy |
| Usability | No IV access<br>No infusion pump<br>No reliable pEEG measurement<br>No plasma or effect site monitor<br>No absolute reliable TCI model<br>Pain on injection<br>Potential for interstitial or disconnected IV access<br>Propofol phenol derivative is not environmentally friendly<br>Unused and wasted propofol increases cost<br>Syringes and tubing are expensive and not environmentally friendly |

PRIS – propofol-related infusion syndrome, $CST_{½}$ – context-sensitive half-time, IV – intravenous, pEEG – processed EEG, TCI – target-controlled infusion

following a three-compartment model. The initial distribution from the systemic circulation/plasma (central compartment with a volume V1 and concentration C1) to the brain and liver. There is then distribution to the brain, liver, abdominal viscera and muscles (peripheral compartment with volume V2 and concentration C2, rapidly equilibrating/highly perfused compartment), then eventual distribution to the scarcely perfused/slow equilibrating compartment (the other peripheral compartment with volume V3 and concentration C3) but much larger compartment which is made up of adipose tissue. The rate constants for elimination from plasma K10 represents excretion, and K12 and K13 represent redistribution to compartments 2 and 3 respectively. The values K21 and K31 represent movement of the drug back into the central compartment (Figure 1).[6,8,9] The half-lives for each of these compartments are 2–4 minutes, 30–45 minutes and 3–63 hours respectively.[6]

**Neonatal** pK show high variable and nonlinear changes in the volume of distribution and clearance. They have significantly decreased and widely variable clearance. This clearance does not increase until three months to one year of age, due to the maturity of liver enzymes; subsequently neonates take longer to wake up.[2,4,6] The nonspecific blood esterases that metabolise remifentanil are mature at birth with clearance of the highest in neonates, and decreasing with age to reach adults rates in adolescents.[2]

**Children** have a much larger central compartment and volume of distribution in comparison to adults, and therefore require an increased bolus dose and higher initial infusion rate. Once the peripheral compartments are filled, a lower infusion rate, similar to adults, is needed to maintain anaesthesia. Hepatic glucuronidation and renal excretion are responsible for the elimination of the drug from the central compartment. Clearance of propofol is higher in children, which contributes to the requirements of an increased infusion dose.[5,6]

**Adolescents** can be grouped as small adults. Adult regimens can be used, such as Bristol (10-8-6 regimen).[3]

In the **obese** child, induction doses for propofol are related to lean body weight, whereas, during maintenance, it is more closely related to total body weight, reflecting equilibrium to and subsequent clearance from the third compartment. This may result in potential awareness if there is no effect site monitoring of propofol concentration.[6]

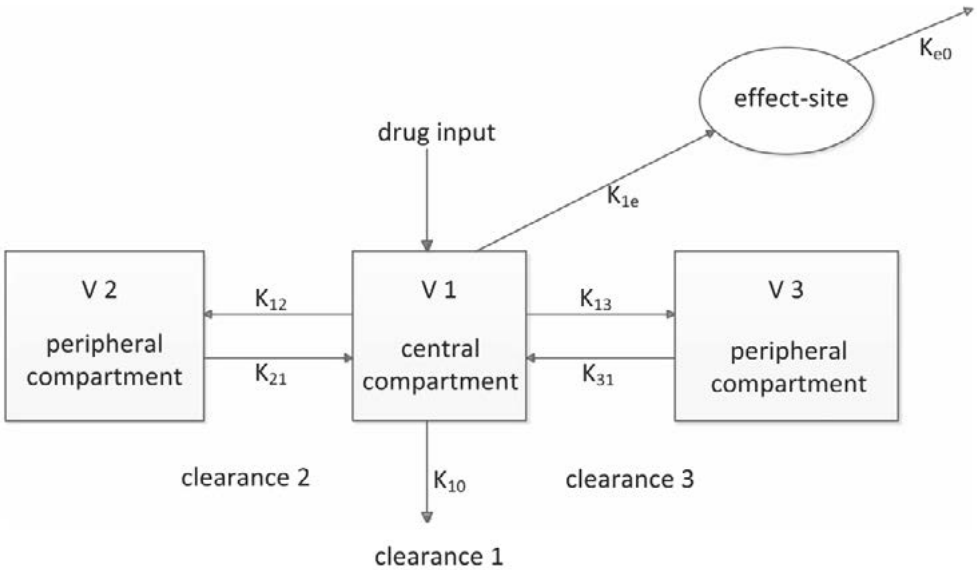


**Figure 1:** The three-compartment model showing the various compartments and their associated rate constant; Keo represents the rate constant for equilibration between plasma and effect-site concentrations[1,8,9]

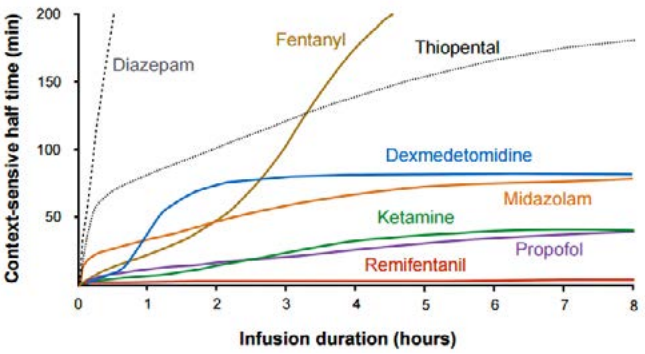


**Figure 2:** Graph depicting context-sensitive half-times of different intravenous agents[12]

The bolus-elimination-transfer (BET) principle was designed to accommodate the three-compartment model and deliver a constant but unmeasured effect site concentration of 3 ug/ml of propofol. The regimen involves a 1 mg/kg bolus dose to rapidly raise effect-site concentrations and induce unconsciousness, followed by an infusion of 10 mg/kg/hr for the first 10 minutes, 8 mg.kg/hr for the next 10 minutes, continuing with 6 mg/kg/hr for the rest of the duration of the surgery. Prolonged infusions result in a long and variable context-sensitive half-time (CST½) range from 8–25 minutes at four hours, increasing to 12–46 minutes after 12 hours of steady-state infusion (Figure 2).[6,10,11]

The current TCI models replicate the principles of the BET regimen to continuously adjust the infusion rate to maintain the estimated plasma concentration. The models determine the estimated Vd for each of the three compartments; calculates the bolus/loading dose, initial infusion rate, and subsequent maintenance infusion rate based on the programmed age and weight. However, it is important to note that earlier models display plasma and not effect-site levels. There is a demonstrated delay in the relationship between plasma concentration and clinical effect.[6] Propofol should ideally be dosed according to the clinical situation. Consideration must also be taken of the inter-individual pharmacokinetics variability related to the large central compartment and the high clearance rate in children. Many manual infusions schemes have been suggested, as well as TCI models (Table III, IV, V, VI).

It should be noted that paediatric TCI works on plasma site concentration (Cp) rather than effect site concentration prediction (Ce). Clinicians need to consider this and allow some time to allow Cp-Ce equilibration when increasing or decreasing target levels.

**Table III:** McFarlan propofol manual infusion scheme, based on the Kataria pK parameter estimates for children between the ages of 3–11 years[2,5]

| Induction dose | Maintenance dose | | | | |
|---|---|---|---|---|---|
| | 0–15 minutes | 15–30 minutes | 30–60 minutes | 1–2 hour | 2–4 hour |
| 2.5 mg/kg | 15 mg/kg/hr | 13 | 11 | 10 | 9 |
| | 250 ug/kg/hr | 215 | 185 | 165 | 150 |

**Table IV:** Steur propofol manual infusion scheme, adapted from clinical observations in children < 3 years of age[2,5]

| Age | Induction dose | Maintenance infusion | | | | | |
|---|---|---|---|---|---|---|---|
| | | 0–10 minutes | 10–20 minutes | 20–30 minutes | 30–40 minutes | 40–100 minutes | > 100 minutes |
| < 3 months | 3–5 mg/kg | 25 | 20 | 15 | 10 | 5 | 2.5 |
| 3–6 months | 3–5 mg/kg | 20 | 15 | 10 | 5 | 5 | 2.5 |
| 6–12 months | 3–5 mg/kg | 15 | 10 | 5 | 5 | 5 | 2.5 |
| 1–3 years | 3–5 mg/kg | 12 | 9 | 6 | 6 | 6 | 6 |

**Table V:** Suggested TCI or infusion rates for propofol with remifentanil[2]

| | Minor surgery (spontaneous ventilation) | Minor surgery (positive pressure ventilation) | Major surgery (positive pressure ventilation) |
|---|---|---|---|
| Propofol TCI | 2.5–4 ug/ml* (2–3 ug/ml for sedation) | 2.5–4 ug/ml* | 3–5 ug/ml |
| Remifentanil (ug/kg/min) | 0.05–0.2 ug/kg/min | 0.2–0.3 ug/kg/min | 0.3–0.5 ug/kg/min |
| Remifentanil TCI | 1–2 ng/ml | 2–4 ng/ml | 3–6 ng/ml |

*A lower limit of 2 ug/ml can be used in conjunction with depth of anaesthesia monitoring

**Table VI:** Propofol TCI models

| TCI model | Target Cp value | Input data required to setup | Notes |
|---|---|---|---|
| Schnider | Propofol (sole agent) 4–8 um/ml<br>Propofol + adjunct (e.g. regional anaesthesia or opioids) 3–4 um/ml (*this excludes neuromuscular agents) | Age, height, gender, weight | |
| Marsh | | Age, weight | Suitable ideally for age > 16, weight > 61 kg |
| Kataria | | Age, weight | Suitable for ages 3–16 years, weight 15–61 kg |
| Paedfusor | | Age, weight | Suitable for ages 1–16 years, weight 5–61 kg |
| Eleveld | | | Suitable for broad population ranging from neonates to elderly |

## Propofol-related infusion syndrome

The greatest concern with propofol infusion in the paediatric population has been PRIS. The suggested definition is a life-threatening condition "*which usually occurs in critically ill patients receiving propofol infusions, typically either a high dose (0.5 mg/kg/hr) or of long duration (> 48 hours) and is characterised by one or more of otherwise unexplained metabolic acidosis, rhabdomyolysis, or ECG changes, with or without AKI, hyperkalaemia, lipidaemia, cardiac failure, fever, elevated liver enzymes or lactate*" leading to bradycardia and potential cardiac arrest. The mechanism of PRIS is not well understood. It is postulated it may be related to direct mitochondrial respiratory chain inhibition, impaired mitochondrial fatty acid metabolism, or interact with the cytochrome system resulting in mitochondrial uncoupling.[13]

Associated risk factors include younger age, infusion dose of 4–5 mg/kg/hr for ≥ 48 hours, but can occur at lower doses in susceptible individuals, acute neurological injury, low carbohydrate intake, catecholamine infusion, and corticosteroid usage. The most common clinical presentation was metabolic acidosis with ECG changes, with secondary features of lipidaemia, hyperkalaemia, AKI, fever, cardiac dysfunction, hepatomegaly with deranged transaminases and elevated lactate. Investigations usually show a Brugada-like pattern or ventricular or supraventricular tachycardia, or bradycardia on ECG. On blood gas, there is severe new-onset metabolic acidosis showing an unexplained lactic acidosis, and hyperkalaemia. Management is usually supportive with a focus on the clinical feature and continuous monitoring for early warning signs. Discontinuation of propofol is imperative, as well as ensuring adequate carbohydrate intake (68 mg/kg/min) and carnitine supplementation (theoretical benefit). In certain circumstances, one may need to consider pacing to treat the bradycardia, in some; rare cases may have to consider haemodialysis and haemoperfusion or ECMO.[13,14]

## Adjuncts to propofol

### *Opioids*

**Remifentanil** is highly potent, has a fast onset and a short $CST_{½}$ of 2–3 minutes. This makes it an ideal agent for infusion for prolonged periods of time (Welch). There is an additive effect when remifentanil is used with propofol resulting in a reduction of the required dose of propofol at a dose as low as 25 ng/kg/min. Remifentanil delivered at clinically relevant concentrations has little effect on bispectral index (BIS). The Minto model has an element of safety, and can be used in TCI devices for all ages because both the volume of distribution and clearance decrease with increasing age. The greater Vd in children reduces the peak concentrations of remifentanil after bolus dosing, the increased clearance results in a lower plasma concentration when infused at adult rates expressed as ug/kg/min. The rapid offset, described by the equilibration half-time ($t_{½}$keo which is 1.16 minutes in adults), means that postoperative analgesia needs to be established before the infusion wears off.[2]

**Alfentanil** has a relatively fast onset ($t_{½}$keo 0.9 minutes in adults) and can be administered as a bolus or an infusion with some residual analgesic effect at the end of surgery. It has a longer $CST_{½}$ than remifentanil that increases from 10 to 45 minutes after a 2-hour infusion. The target concentration for propofol/alfentanil combinations are 4.5 ug/ml and 120 ng/ml respectively during maintenance, reducing to 3.5 ug/ml and 90 ng/ml towards the end of surgery. The alfentanil infusion can be stopped 10–15 minutes before the end of anaesthesia.[2] The TCI model described for alfentanil is the Maitre model.

**Sufentanil** has a relatively slow equilibration half-time ($t_{½}$keo of 6.2 min) and a plasma concentration (Cp) of 0.5–3 ng/ml is used for analgesia during TIVA. The pK profile in cardiovascular surgery showed an increased Vd in infants when compared to children and adolescents, while clearance is increased in infancy with reduced values in children (16.9 ml/kg/min) when compared to adolescents (13.1 ml/kg/min). Adult literature has shown that it has better analgesic quality and delayed awakening when compared to remifentanil. Ideally, sufentanil infusions should be stopped approximately 30 minutes before stopping propofol.[2] The TCI model described for sufentanil is the Gepts model.

**Fentanyl** is an unfavourable drug to use as an infusion due to its prolonged $CST_{½}$ during long surgery.

### *Ketamine*

Ketamine is occasionally used as an adjunct or as a sole agent, but it has a long $CST_{½}$ with delayed awakening after prolonged infusion. It however remains popular due to hypnotic, analgesic and cardiorespiratory stability. Plasma concentrations of 3 ug/ml are associated with anaesthesia, and consciousness usually occurs at concentrations < 0.5 ug/ml, while analgesia occurs at 0.2 ug/ml. There is rapid onset after IV administration of ketamine (about 30 seconds) due to it being highly lipid soluble with rapid distribution.[2] If used for prolonged periods, it is recommended that the infusion be stopped at least 30 minutes prior to emergence.

Ketamine can be used as a sole agent at manual infusion rates varying from 0.1–2.5 mg/kg/hr depending on the type of procedure, patient status and other agents used.[5] In order to achieve a concentration of 3 ug/ml, Dallimore et al.,[15] suggest a loading dose of 2 mg/kg followed by an infusion of 11 mg/kg/h (0–20 minutes, 7 mg/kg/hr (20–40 minutes), 5 mg/kg/hr (40–60 minutes) and 4 mg/kg/hr thereafter in children 1.5–12 years of age. Infusions of > 2 hours result in prolonged recovery.

Combined therapy with racemic ketamine and propofol as additive ("ketopropofol") has gained popularity in usage with ratios variable from 1:1–1:5. Dosing of ketopropofol is variable with examples including using a McFarlan manual infusion regimen.

**Table VII:** Manual infusion schemes of the various adjuncts[3]

| Drug | Loading dose | Maintenance infusion | Notes |
|---|---|---|---|
| Propofol | 1 mg/kg | 10 mg/kg /hr for 10 minutes,<br>Then 8 mg/kg/hr for 10 minutes,<br>Then 6 mg/kg/hr thereafter | Adult regimen to achieve 3 ug/ml<br>Under delivers to children and achieves lower blood concentration of 2 ug/ml |
| Propofol | 1 mg/kg | 13 mg/kg/hr for 10 minutes,<br>Then 11 mg/kg/hr for 10 minutes,<br>Then 9 mg/kg/hr thereafter | Can be used concurrently with an opioid |
| Alfentanil | 10–50 ug/kg | 1–5 ug/kg/min | Results in blood concentrations of 50–200 ng/ml |
| Remifentanil | 0.5–1 ug/kg/min | 0.1–0.5 ug/kg/min | Produces blood concentrations of 5–0 ng/ml |
| Sufentanil | 0.1–0.5 ug/kg | 0.005–0.01 ug/kg/min | Results in blood concentrations of 0.2 ng/ml for sedation and analgesia |
| Sufentanil | 1–5 ug/kg | 0.01–0.05 ug/kg/min | Results in blood concentrations of 0.6–3.0 ng/ml for anaesthesia |
| Fentanyl | 1–10 ug/kg | 0.1–0.2 ug/kg/min | |
| Ketamine | 1–3 mg/kg | 0.1–2.5 mg/kg | Smaller dose and infusion rate for analgesia and sedation.<br>Larger dose and infusion rate for anaesthesia titrated to effect |
| Midazolam | 0.05–0.1 mg/kg | 0.1–0.3 mg/kg/hr | |

### *Dexmedetomidine*

Immature clearance in the first year of life and a higher clearance in small children dictate infusion rates that change with age. Dexmedetomidine is an attractive option as an adjunct to propofol TIVA as it has the ability to reduce propofol and opioid requirements, provides moderate hypotension, decreases bloodloss, allows monitoring of evoked potentials, reduces ED but at the expense of prolonged awakening.[2]

### *Midazolam*

The $t_{½}$keo of midazolam is 0.9–1.6 minutes. A midazolam infusion (e.g. 0.05 mg/kg/min, 0.83 ug/kg/min, plasma concentration 125 ng/ml) combined with propofol reduced the clearance of both drugs resulting in a 25% increase in propofol concentration and a 27% increase in midazolam concentration. The combination of these drugs improves haemodynamic stability but delays recovery when compared to propofol alone.[2]

## Monitoring of total intravenous anaesthesia/target-controlled infusion

Open loop TCI occurs when there is no feedback to the pump to manipulate the infusion to the programmed effect/plasma site concentration or depth of anaesthesia. In closed loop TIVA, the infusion is adjusted continuously according to effector site clinical effects using EEG-based depth of anaesthesia monitoring as a feedback control. The advantage of a closed loop system is the ability to accommodate for inter-individual variability seen

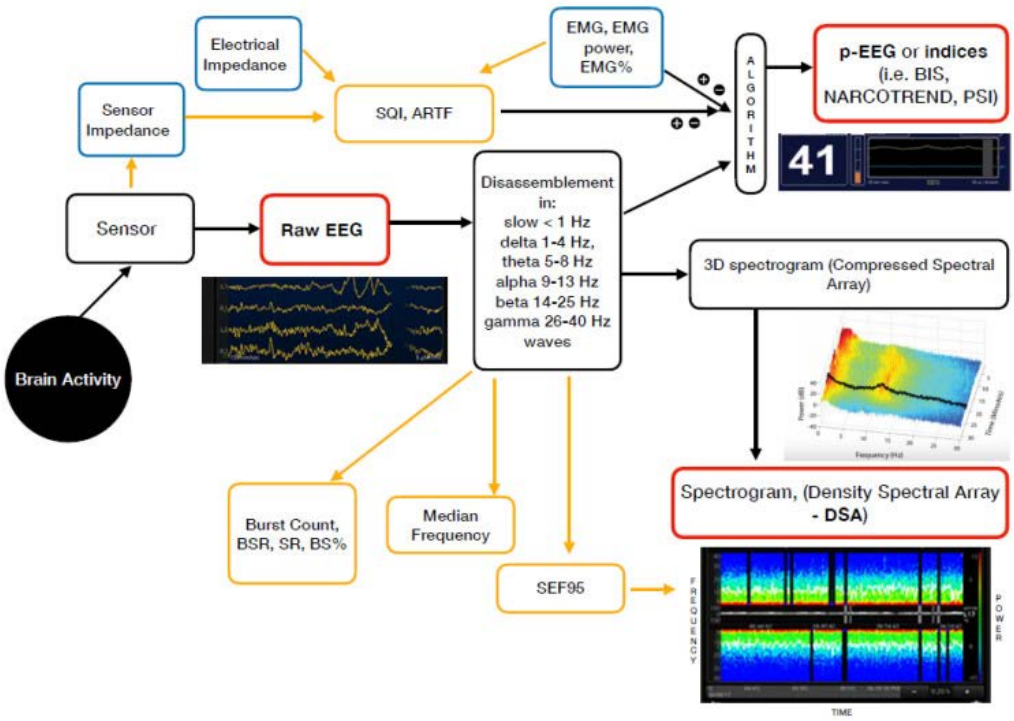


**Figure 3:** Mechanism of action of available EEG-derived anaesthesia monitoring[16]

in children performs more accurately and inevitably enhances patient safety by reducing operator-dependent dosing errors, reduced propofol consumption with subsequent improved respiratory and cardiovascular stability and reduced time to recovery.[6]

Output of the EEG in children is influenced by the depth of anaesthesia, mechanism of action of anaesthetic agents and typical age-related changes of the developing brain. This has affected the validity and application of this monitoring. There is little evidence as to the target processed EEG (pEEG) values for specific procedures, lack of correlation of pEEG values with targeted plasma propofol concentration, lack of reliable pEEG data in children < 1 years of age, inaccuracies in children with neurological disease, and inaccuracies during hypothermia and/or cerebral hypoperfusion. Furthermore, currently available devices are all based on algorithms tested in adults. Despite this, monitoring pEEG is useful to aid titration of propofol used in conjunction with other depth of anaesthesia monitors.[6,16] Besides the unprocessed EEG, there are two different groups of EEG-based devices, the pEEG and the spectrogram or density spectral array (DSA),[16] depicted in Figure 3. Examples of pEEG monitors are BIS monitor, Entropy, Patient State Index (PSI) of the SEDLine brain function monitor or the Narcotrend index.

Most EEG-derived monitors disassemble a complex raw EEG waveform into a series of waves of different frequencies. This is then converted into a single index through mathematical algorithms resulting in the pEEG. This index can be affected by the electromyogram (EMG) and the signal quality index (SQI or ARTF). The spectrogram is a real-time monitor, which portrays all the EEG frequencies and their power over the time in a 3-D spectrogram or compressed spectral array. The latter is then integrated into a 2-D plot using colours to represent the different powers in the DSA. Other derived parameters are spectral edge frequency (SEF95), median frequency and the burst count (burst/minute), suppression rate (SR), burst suppression rate (BSR) or BS% indicator (burst suppression percentage). These can be displayed numerically or visualised on the spectrogram.[16]


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