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This presentation focuses on age-related changes in pharmacokinetics (PK) and pharmacodynamics (PD) of anaesthetic agents used during general anaesthesia in children. The section is divided into inhalational agents and intravenous anaesthetic agents.

INHALATIONAL AGENTS**BASIC PHARMACOLOGY**

Not only the required concentration of inhalational agents to induce anaesthesia but also the wash-in characteristic of these agents depend on age. MAC values of most inhalational agents peak at 6-12 months of age and the MAC values are close to each other in neonates and adults. Only sevoflurane does not have a decreased MAC value in neonates compared to infants [1]. In general, the dose-effect relationship of all inhalational agents is very steep: if 1.0 MAC is regarded as an ED₅₀, then an ED₉₅ would be 1.2 MAC. However, the required concentration depends on the procedure for which anaesthesia is administered. E.g. one MAC is required to insert a laryngeal mask and 1.4 MAC for endotracheal intubation.

Wash-in of all inhalational agents depends on several age-related factors. High concentration of nitrous oxide produces rapid rate of increase of alveolar to inspired concentration that is even more rapid in neonates than in adults. More importantly, the high ratio of alveolar ventilation to functional residual capacity in neonates and infants compared to adults promote the rapid wash-in of all inhalational agents in these young individuals. As a greater proportion of cardiac output is distributed into the vessel-rich group in infants compared to adults the equilibration of inhalational agents is reached faster in infants, the effect being promoted by infants' high cardiac output. The slightly lower blood solubility and significantly lower tissue solubility of inhalational agents in neonates compared to adults also contribute to the rapid tissue equilibration of these agents in neonates and infants.

If a circle system is used to induce anaesthesia then some time constants are important to know. The time taken to fill the circle system plus the functional residual capacity represents one time constant (T). If these volumes equal fresh gas flow in minutes (e.g. 3 litres and 3 l/min), then T = 1 min. In one T the circle concentration is 63 %, in 2 T 86 % and in 3 T 95 % of the fresh gas concentration. This means that if the vapouriser concentration is set from 0 to 7 % at time zero, then the circle concentration is 4.4 %, 6.0 % and 6.6 % after one, two and three minutes, respectively.

METABOLISM

Metabolic pathways of inhalational agents are similar in infants and adults. Cytochrome P450 isozyme system is responsible for the metabolism and produces inorganic (sevoflurane, enflurane) or organic (halothane, sevoflurane) fluoride. In general, the hepatic metabolic rate of inhalational agents increases during infancy to reach adult rates by two years of age. The metabolism is greatest with halothane (20 %), much less with sevoflurane (5 %) and least with isoflurane (0.2 %) and desflurane (0.02 %).

Peak fluoride concentrations produced by sevoflurane are dose-dependent and similar in children and adults. There are no reports of renal toxicity of inorganic fluoride produced by sevoflurane in children and it seems justified to use sevoflurane also in children with moderate renal failure.

The hepatic toxicity of halothane is extremely low in children and there is no evidence against administration of repeated halothane anaesthesia in children. Other inhalational agents have also been described to produce hepatic toxicity at a very low incidence.

CLINICAL EFFECTS

Nitrous oxide augments MAC values of inhalational agents in infants and children like in adults. For unknown reasons the augmentation seems to be less when sevoflurane or desflurane are used compared to other inhalational agents (25 vs. 60 %) [2].

All inhalational agents do depress myocardial contractility and cardiac output. However, these effects are specific for each agent. Cardiovascular depression and dysrhythmias produced by sevoflurane are significantly less than those produced by halothane, both in infants and in children [3-5]. Infants have a greater incidence of dysrhythmias than older children.

Inhalational agents depress the ventilation more in infants than in children. Sevoflurane is the agent with the least respiratory depressive effect among all inhalational agents [6]. Sevoflurane has been shown to produce epileptiform activity during induction of anaesthesia even though there are only few case presentations on the subject [7].

CLINICAL USE

To induce anaesthesia *via* a facemask all suitable inhalational agents can be administered by a stepwise incremental increase method or by a single-breath vital capacity induction method. The latter method is much quicker and several institutions favour this technique. If 7 % sevoflurane is used together with nitrous oxide in oxygen, then endotracheal intubation can be successfully achieved within 3.1 minutes in infants and 4.0 minutes in older children. Under equipotent concentration of halothane respective times are 4.1 and 5.5 min [5].

Desflurane is not a suitable agent for mask induction due to very high incidences of breath holding, laryngeal spasm and desaturation [8]. The relatively high incidence of isoflurane-induced laryngeal spasms during induction has also restricted the use of this agent for induction of anaesthesia in children [9]. Halothane and sevoflurane are the most suitable agents for mask induction.

For maintenance of anaesthesia, most inhalational agents can be used. Desflurane produces a sympathetic discharge when the concentration is rapidly increased and may thus mimic blood pressure and heart rate increases seen when the level of anaesthesia is unsatisfactorily low. Isoflurane and sevoflurane are excellent agents for maintenance of anaesthesia. Many institutions favour halothane for maintenance of anaesthesia in children due to its relatively low cost. The depth of anaesthesia can be accurately monitored e.g by BIS-monitoring in both infants and children [10].

All inhalational agents augment the effects of non-depolarising muscle relaxants. The augmentation is greatest with sevoflurane (60-70 % decrease in the requirement of a muscle relaxant) and least with halothane. This augmentation, however, is not an all-or-none phenomenon but consists of a clear time- as well as age-dependent fashion: it takes 60-90 minutes to establish full augmentation and this augmentation is reached faster in infants than in older children [11].

Sevoflurane has as a major drawback the characteristic to promote excitation after anaesthesia. The aetiology of this excitation is unknown. It can be treated but not prevented by iv-anaesthetics or sedative agents and by taking proper care of postoperative pain [12].

INTRAVENOUS ANAESTHETIC AGENTS

THIOPENTONE

Pharmacokinetics of thiopentone can be characterised by a three-compartment model. The drug is highly lipophilic and crosses the blood-brain barrier easily. The free fraction in plasma is 14-26 %. It induces sleep within one circulation time (in 25 seconds in neonates and in one minute in adults). Plasma clearance of thiopentone is greatest in young children but recovery to consciousness following a single dose is equally rapid in all age groups. Recovery of consciousness following an induction dose of thiopentone takes place within 5-10 minutes. Rapid recovery is caused by the redistribution of the drug from the vessel-rich compartment to fat and muscle tissues. After the neonatal period there is no great change in its volume of distribution (table 1). Thiopentone has a capacity-limited elimination and a low hepatic extraction ratio (0.20). Its elimination takes place *via* oxidation and desulfurisation in the liver. Final elimination half time is very long especially in neonates (table 1) [13].

TABLE 1. PHARMACOKINETIC DATA OF THIOPENTONE

	Neonate	Child	Adult
Volume of distribution (l/kg)	3.6	2.1	2.2
Elimination half-time (h)	36	6	12
Clearance (ml/kg/min)	1	7	3

Thiopentone is a potent hypnotic agent that inhibits opening of chloride-channels and potentiates inhibitory effects of GABA(A) receptors in the central nervous system. The ED₅₀ of thiopentone has a clear age dependent pattern in that neonatal and adult requirements are close to each other while infants require a 60 % greater dose (4 vs. 7 mg/kg) [14]. It is noteworthy that infants have a greater variation in thiopentone requirements than older children [14]. Infusion requirement of thiopentone to maintain anaesthesia e.g. for MRI examination is 8-12 mg/kg/h.

Thiopentone produces a reduction in blood pressure and in myocardial contractility and a significant ventilatory depression if injected rapidly. It may also produce dysrhythmias and bronchoconstriction. Respiratory depression, apnoea, laryngospasm, cough and hiccup can in most cases be avoided if the drug is injected slowly (within 2-3 minutes). Thiopentone is diluted into a 2.5 % solution that is very alkalotic (pH 10.5).

During recovery from thiopentone anaesthesia some patients may express delirium, confusion or prolonged somnolence. It may also produce nausea and vomiting and postoperative shivering.

PROPOFOL

Propofol is also characterised with a three compartment pharmacokinetic model. The drug is highly lipid soluble and it easily diffuses across the blood brain barrier. It is highly protein bound and its free fraction in plasma is only 3 %. It induced sleep within 30-40 seconds. Propofol has a hepatic extraction ratio close to 1.0 and is metabolised via the cytochrome P450 2C9 subsystem. Propofol's volume of distribution is very large (table 2) and its clearance is greater in children than in adults [15]. On average, the clearance is 10 times greater than that of thiopentone. Elimination half time is shorter in children than in adults but this difference does not have a clinical significance since the recovery following a single dose or short time infusion is rapid (in 5-10 minutes) in all age groups.

TABLE 2. PHARMACOKINETIC DATA OF PROPOFOL

	Child (1-3 yr.)	Child (3-10 yr.)	Adult
Volume of distribution (l/kg)	9.5	7.2	4.7
Elimination half-time (h)	3.1	3.6	5.2
Clearance (ml/kg/min)	53	32	28

Propofol is prepared into 1 or 2 % isotonic lipid emulsion containing EDTA as a preservative to prevent bacterial growth. The solution is slightly alkalotic (pH 8.0). It is contraindicated in patients allergic to soybean or eggs. Propofol induces pain when injected into a vessel and the sensation may be severely burning and irritating. Lidocaine 1 mg/kg before propofol or small dose of alfentanil alleviates the pain significantly or prevents it completely.

For maintenance of anaesthesia, a continuous infusion can be applied. To maintain a constant drug concentration in the central compartment, the infusion rate should be adjusted based on time so that the rate is greatest at an early phase of infusion decreasing stepwise by 30-40 % within one hour. Initial infusion rate may be 15 mg/kg/h to decrease to 12 mg/kg/h within 30 minutes and to 10 mg/kg/h in 90 minutes. This reduction of infusion rate is related to the drug's context sensitive half time that is prolonged during long infusion, from 10 to 20 minutes in children and from 7 to 10 minutes in adults during a three hour infusion period (table 3) [16].

Propofol is a hypnotic agent having its effect at least partially *via* GABA(A) receptors. ED₅₀ of propofol has a clear age related pattern similar to thiopentone even though the differences are smaller. A single dose

required by young infants is 3-4 mg/kg and in older children 2-3 mg/kg. Like for thiopentone, the variation in propofol requirement is much greater in infants than in children. Recovery of consciousness and of psychomotor skills is faster after propofol than after thiopentone in all age groups.

Propofol induces a decrease in blood pressure which is more pronounced if the drug is injected rapidly or given to compromised patients. However, the myocardial depression is less than that produced by thiopentone. If propofol is given to patients with prolonged QT interval, it may induce significant bradycardia. On an average, the haemodynamic response to endotracheal intubation or laryngeal manipulation is better suppressed by propofol than by thiopentone. Propofol may induce respiratory depression, apnoea or laryngospasm especially when administered rapidly. It has been shown to induce seizure-like movements and has induced convulsions.?

Propofol has a significant anti-emetic effect that can be beneficial also in long-term infusion of the drug. However, infusion of propofol cannot be applied for several days due to the possible associated morbidity [17]. As a single dose propofol can be used in all age groups of infants and children.

TABLE 3. CONTEXT SENSITIVE HALF TIME OF PROPOFOL

	1 h	2 h	3 h
Children (3-11 yr.) (min)	10.4	12.9	19.6
Adults (min)	6.7	8.0	9.5

KETAMINE

Pharmacokinetics of ketamine can be characterised with a two-compartment model. Ketamine is water-soluble but as it remains mostly non-ionised, it crosses easily the blood brain barrier to induce sleep within one minute. Ketamine has two enantiomers, S(+) and R(-), the S-enantiomer being active. Hypnotic effect is mediated *via* NMDA receptor antagonism.

Like with thiopentone and propofol, ketamine is initially distributed to the vessel rich compartment and then redistributed to muscle tissue. Recovery from ketamine anaesthesia is difficult to evaluate due to psychodysleptic effects but the effects of a single dose seem to last for 5-12 minutes. Volume of distribution is similar in all age groups. It has a high hepatic extraction ratio and its metabolism *via* cytochrome P450 family is decreased in neonates to produce relatively long elimination half time (table 4).

TABLE 4. PHARMACOKINETIC DATA OF KETAMINE

	Neonate	Child	Adult
Volume of distribution (l/kg)	3.7	2.8	3.0
Elimination half-time (h)	3.1	2.1	2.6
Clearance (ml/kg/min)	14	22	17

Ketamine is a poor hypnotic agent and a much stronger analgesic agent. It also produces good amnesia. During induction of anaesthesia it may produce involuntary muscular movements that mimic epileptic convulsions. It decreases myocardial contractility but maintains blood pressure especially when administered slowly due to its sympathomimetic action. It produces characteristic bronchodilatation.

Ketamine is associated with a high incidence of postoperative nausea and vomiting that often requires proper treatment. Characteristic of ketamine are perceptual illusions and vivid dreams that are even more common in adults but still warrant use of benzodiazepine together with ketamine in children [18]. Ketamine induces sialorrhoea that is abolished if prophylactic glycopyrrolate is given. Ketamine protects pharyngeal and laryngeal reflexes more than other intravenous anaesthetic agents.

Normal induction dose of racemic ketamine is 2-3 mg/kg iv. If a S-enantiomer is used, then the dose is 50% of the racemic dose. For continuous infusion a dose of 2-3 mg/kg/h of racemic and of 1-2 mg/kg/h of S-enantiomer may be used. If ketamine is used as an i.m. injection then the deltoid muscle is favoured due to its high vascularization and low required induction dose (3-4 mg/kg of racemic ketamine) when administered into this muscle.

ETOMIDATE

Etomidate is a very potent hypnotic agent that is used relatively rarely even though it has some distinctive advantages over other agents [19]. R(-) enantiomer possesses the hypnotic activity that is produced within one circulation time following a dose of 0.2-0.3 mg/kg. The anaesthesia will last for 10 to 20 minutes after a single dose of etomidate. Typical for etomidate is a three compartment pharmacokinetics with clear redistribution to terminate the central nervous system effects of the drug. Typical for a lipophilic drug, distribution volume is greater than the body size. Clearance is 60 % of hepatic blood flow and elimination takes place via hepatic esterase hydrolysis.

Etomidate is solubilised into a mixture of water and propylene glycol. The final solution has high osmolality of 4900 mOsm/l. Even though etomidate does not liberate histamine, this high osmolality may induce histamine liberation in susceptible patients. Intravenous injection of etomidate is associated with local pain as with propofol. Etomidate has been widely used for short procedural anaesthesia [20].

Etomidate may decrease cardiac output due to decreased heart rate without affecting myocardial contractility. In contrast to propofol, etomidate maintains baroreceptor responsiveness. Etomidate does not normally depress ventilation if no opioid has been administered to the patient. Etomidate possesses both anticonvulsant and epileptiform effects, the net effect being patient specific.

Long term infusion of etomidate is associated with decreased cortisol and aldosterone concentrations which may prevent its use to sedate patients in the ICU. The suppressed stress response induced by etomidate may be used for cardiac surgery to improve metabolic response to surgery and cardiopulmonary bypass.

TABLE 5. PHARMACOKINETIC DATA OF ETOMIDATE

	Neonate	Child	Adult
Volume of distribution (l/kg)	unknown	2.8	2.2
Elimination half-time (h)	6.0	2.9	3.5
Clearance (ml/kg/min)	unknown	17	13

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