INTRODUCTION

Millions of anesthetics are delivered worldwide to children daily. One commonality amongst these anesthetic practices is that independent of the city or country, almost all include provision for inhalational anesthesia. Whether used for induction or maintenance of anesthesia, inhalational anesthetics are pervasive because they are effective, reliable, safe, easy to deliver, stable, and without major end-organ sequelae. Among inhalational anesthetics that are available for use today in children: sevoflurane and isoflurane. [1]

Key points supporting inhaled anesthesia

- Each inhalational anesthetic satisfies the four pillars of anesthesia.
- Induction is easy without i.v. access.
- Induction of anesthesia is quick, simple and pain-free by mask.
- Easy to estimate blood tension of inhalational anesthetics noninvasively.
- Intravenous agents demonstrate excessive inter-individual variability and cannot be estimated.

The four pillars of general anesthesia are loss of consciousness⁄ amnesia, analgesia, ablation or blunting of autonomic reflex responses, and muscle relaxation. [32] Potent inhalational anesthetics satisfy all four pillars to varying degrees. They induce loss of consciousness (with limited response to pain), amnesia, blunt reflex responses, and potentiate muscle relaxants. In contrast, propofol induce anesthesia, may cause amnesia, partially blunt autonomic reflex responses and do not potentiate muscle relaxants. Thus, each of the potent inhalational anesthetics satisfies the four pillars of a complete anesthetic. The delivery of inhalational anesthetics to the lungs provides an extremely rapid delivery of drug to the brain. Using the overpressure technique for soluble agents or the target inspired concentration for insoluble agents, the wash in of anesthetics to the alveoli and thus the brain (via the arterial circulation) is particularly rapid in infants and children. In contrast, the i.v. agents are delivered through an i.v. route and are diluted in the venous circulation before passing through the heart to reach the brain and other vessel rich organs.Several layers of safety measures are incorporated into the monitoring systems to verify the delivery of inhalational anesthetics including maximum deliverable concentrations from the vaporizer and breath-by-breath measurement of the inspired and expired inhalational concentrations, which are not commercially available for i.v. drugs. Maximum and minimum concentrations for each anesthetic may be programmed into the monitor to ensure an adequate dose of anesthetic is delivered. Even when an agent analyzer is not available, measuring the oxygen and carbon dioxide concentrations in the breathing circuit confirms the integrity of the circuit.[1] Hence، these monitoring strategies provide a safety net that alarms when the inhalational anesthetic concentrations are outside the accepted range.In contrast, there is no similar safety net for i.v. agents.There is no mechanism to detect a disconnect in the i.v. line [2] or extra-venous infusion of i.v. agents before awareness occurs during surgery in the paralyzed child or if movement occurs in the non-paralyzed child. This is particularly troublesome in children as the arms are frequently tucked under the drapes thus concealing the i.v. site. There are no alarms that sound during TIVA when either excessive or inadequate doses are administered.

The depth of anesthesia can be quantified during inhalational anesthesia by measuring the end-tidal partial pressure of the anesthetic (using agent analyzers). Steady-

state measures of potency, the minimum alveolar concentration (MAC) have been determined for all inhalational anesthetics and in infants and children. [3–5] Agent analyzers are present in virtually every location where inhalational anesthetics are administered. Hence, a child's individual depth of anesthesia can be measured during every anesthetic without additional costs, even during interventions [i.e., skin incision، laryngeal mask airway (LMA) insertion]. As well، we can determine the dose to attenuate adrenergic responses and awareness. In contrast, similar measurements for the i.v. drugs are not available.

There is no MAC for i.v. drugs, no measure of the MAC-multiples of i.v. drugs that confers amnesia and no measure of the equivalent MAC-multiples to confer general anesthesia in children of different age groups.

The second method to assess the depth of anesthesia is the depth of anesthesia monitor of which there are several. In the case of the bispectral index monitor (BIS) (Aspect Medical Systems, Norwood، MA, USA); the algorithm was developed from adult electroencephalogram (EEG) patterns and with anesthetics other than sevoflurane. These monitors may not be reliable in children <5 years of age. [6] When applied to children anesthetized with sevoflurane، the BIS failed to predict movement, showed large inter-individual variability and the reading actually increased at concentrations between 3%and 4%.[7,8] To assess the depth of anesthesia during TIVA, >30% of the BIS reading was explained by the estimated propofol concentration.[9] In summary, agent analyzers can estimate the depth of anesthesia during inhalational anesthesia but in the case of TIVA, there is no reliable measure.Awareness during anesthesia in children piqued readers' interest lately after publication of several occurrences. For the most part, these reports can be explained by lapses in an appreciation of the pharmacology of sevoflurane. [9] Sevoflurane's limited solubility reduces its potency. As a consequence، recovery from anesthesia is rapid whether it occurs when a child is briefly disconnected from the circuit during transport or when the child is painfully stimulated soon after induction or after the anesthetic concentrations were reduced.[10,11] Failure to supplement the anesthetic or to wait for an adequate depth of anesthesia may prompt similar occurrences.

In the case of i.v. induction, the actual blood and brain concentrations of propofol (or any other drug) cannot be accurately measured in real time or noninvasively for real-time feedback as in the case of inhalational anesthetics. Although we can administer a specific dose of an i.v. drug to a child, we are unable to measure its blood or brain concentration noninvasively.

In the case of intravenous induction, i.v. access must be established before i.v. drugs can be administered. If EMLA is used, this takes up to 1 h to prepare the skin for the i.v. In many practices, the children are not present in the preoperative holding area in sufficient time to allow EMLA to be fully effective. EMLA not only topicalizes the skin, but it blanches the skin leading to venoconstriction and difficulty visualizing the veins in the hand. Ametop® (Smith & Nephew Inc. St. Laurent, Quebec, Canada), which anesthetizes the skin more rapidly than EMLA and causes no venoconstriction, is available in Europe and Canada but not in the US. [1] Despite reassurances that these and other techniques permit a 'pain-free' i.v. insertion, most children around the world fear the dreaded 'i.v.' to circumvent this fear, anesthesia is commonly induced by mask. Once an adequate depth of anesthesia has been achieved, i.v. access can be secured. [1]

Tracheal intubation

Intubation of the trachea using direct laryngoscopy can be performed without any neuromuscular blocking drug. Intubating conditions then depend on the depth of anaesthesia (i.e. the type, the dose, or the combination of anesthetics) and are related to time interval between the injection of anesthetics and laryngoscopy. [12]

Muscle relaxants are widely used to facilitate tracheal intubation but are never used without anesthetics. In this case, the quality of tracheal intubation depends on relaxation induced by abolition of upper airway reflexes related to central nervous system depression induced by IV or inhaled anesthetics, and by paralysis of the laryngeal muscles induced by muscle relaxants. The onset time of paralysis is different from a muscle relaxant to another and from muscle group to another and from one muscle group to another (adductor pollicis vs. laryngeal adductor muscles). [12] This onset time is directly related to the dose and inversely related to potency for non depolarizing relaxants. It is 60 sec for Succinylcholine[13,14] and rocuronium with a dose superior to 1.0 mg/kg and it is superior to two minutes for vecuronium, atracurium and rocuronium with a dose of twice the ED_{95}.[15]

The longer the onset time of the muscle relaxant, the longer is the time interval between the administration of anesthetics and tracheal intubation if intubation is performed with respect to muscle paralysis. The clinical consequence of this delay is a decrease in the depth of anesthesia at the time of laryngoscopy.

The longer the time interval between the induction of anesthesia and intubation, the more important is muscle paralysis to obtain clinically acceptable intubating conditions. However, the interaction between various doses of induction drug and a muscle relaxant of intermediate onset time of action on intubating conditions in the clinical setting remains unclear. [15]

Rocuronium

Rocuronium is a non-depolarizing aminosteroid muscle relaxant. In clinical studies its most impressive features are the rapid onset time and, more importantly the rapid development of good intubating conditions it gives at normal intubating doses. Rocuronium is 15%as potent as vecuronium. [16]

Chemistry

Rocuronium, the 2 morpholino, 16 allyl pyrrolidno, 3 desacetyl derivative of vecuronium, it is a steroidal neuromuscular blocking agent (figure) resembling vecuronium in its time-course of neuromuscular blocking action. [16]

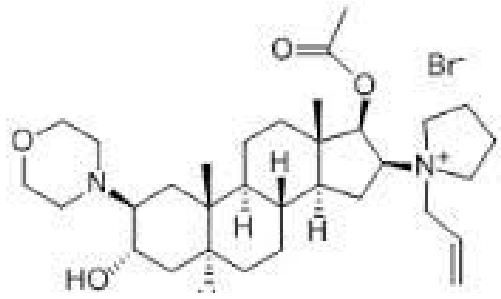

Figure (1): Rocuronium chemical structure

The pharmacokinetics of rocuronium is characterized by a smaller volume of distribution. The smaller distribution volume of rocuronium may be a reflection of the lower lipophilicity of this compound. (17)

Onset and distribution:

The onset time of rocuronium i.e. the time from injection of the drug to maximum effect, is faster than that of all available non-depolarizing neuromuscular blocking agents.(18) for any comparable dose of a non-depolarizing neuromuscular blocking agent, rocuronium can be expected to provide paralysis and satisfactory intubating conditions more rapidly.

Duration of action:

The clinical duration of action of rocuronium is proportional to the dose given.

Administration and use:

Rocuronium is a non-depolarizing neuromuscular blocking agent that has a relatively fast onset of neuromuscular blockade. Its low potency requires administration of larger dose. This allows effective buffered diffusion and more rapid occupancy of large numbers of receptors and non specific binging sites. This onset time of rocuronium is significantly shorter than equivalent doses of any other non-depolarizing neuromuscular blocking agent previously studied. (19)

It is administered through intravenous route (I.V.). The standard intubating dose is 0.6 mg kg^{-1} provides good to excellent intubating conditions within one minute in nearly all patients at this dose general muscle paralysis adequate for any type of surgery is established within two minutes, with subsequent incremental doses of one quarter this amount. Because rocuronium induced neuromuscular block occurs faster at the adductor of larynx (although the block is less intense) than at the adductor pollicis muscle, it appears that intubation may be performed before complete block obtained at the thumb. (20)

The drug is non cumulative with repeated administration and that feature has made it possible to use it as a continuous infusion for longer surgical procedures by a rate of 0.3-0.6 mg/kg/hour. (21)

Midazolam

Midazolam belongs to a new generation of benzodiazepines called Imaidazobenzodiazepines with wide toxic/therapeutic ratio and safety margin, and does not produce prolonged sedation associated with other benzodiazepine such as diazepam. [22]

The term "benzodiazepine" refers to the common chemical structure shared by all of the compounds within this class of drugs. The site of action for benzodiazepines are specific receptors in the central nervous system (CNS) associated with GABA receptors. Benzodiazepinesreceptors have been identified in different body tissues including the heart and skeletal muscles, though the predominance appears to be in the central nervous system. The low incidence of respiratory depression with benzodiazepines may be related to the low density of binding sites in the brain stem. [23]

Benzodiazepines have been widely used for premedication. Principal advantage of this class is their relative safety, availability of antagonist, selective anxiolytic activity and ability to produce anterograde amnesia. Benzodiazepines may indirectly elevate the patient's threshold of pain. This does not mean that they are analgesics, but the patient appears to reach a state of indifference. [23]

A. Chemical structure

Midazolam consists of a benzene ring fused to a 7 membered diazepine ring. The Midazolam molecule solubility is PH dependent. At a PH>4.5, the molecule exists almost entirely in the lipophilic closed-ring form. As the PH decreases, the relative proportion of the open-ring form increases, such that at a PH of<2.5, the open ring predominates. When it is injected, the slightly alkaline (PH about 7.4) environment of the blood stream causes the imidazoline ring to close, and it becomes more lipid soluble, facilitating its rapid uptake into nerve tissue. [24, 25]

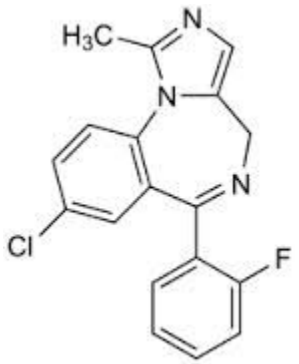

Figure (2): Midazolam chemical structure

B. Routes of administration:

1) Parentral:

When used in intravenous or intramuscular sedation, the dosage should be titrated in small increments to provide optimal premedication according to the patient's age, clinical status, and psychological state. [26]

IM dose is 0.07 mg/kg and its effect starts to appear after 5 min, the peak is reached within 20-30 min. however, after IV administration clinical effect starts to appear at the end of injection and reaches its peak after 3 min with dose of 0.5-1 mg. [23, 26]

2) Intranasal:

Midazolam is effective intranasally in doses ranging from 0.2-0.6 mg/kg with bioavailability approximately 55%. The rate of onset and recovery are more rapid. A major adverse effect of intranasally administered Midazolam is irritation of the nasal passages. [27]

3) Sublingual:

Midazolam can be administered sublingually at the same dosage as intranasally. It may be difficult to prevent small children from either swallowing the Midazolam or spitting it out immediately. It has an advantage of mucosal absorption directly into the systemic circulation with no first pass hepatic metabolism due to the rich blood supply of oral mucosa, has rapid action, reliable predictable effect and the drug is not destroyed by the gastrointestinal enzymes. [27,28]

4) Rectal:

The advisable Midazolam dose for rectal application is 0.25-0.35 mg/kg. The first pass metabolism in the liver is largely avoided with this route of administration. The bioavailability of rectal Midazolam is 52% with the sedative reaching a peak plasma concentration within 20 min. [28]

5) Oral:

It can be given in a dosage of 0.25 mg to 1.0 mg/kg up to total dose of 20 mg depending on the duration of surgery and the anxiety level of the child. The bioavailability of oral Midazolam is 44% as a result of first pass metabolism, with a peak plasma concentration within 30 min. [29]

Before 1998, however, there was no commercially prepared oral formulation available on the US market. Before the release of versed syrup by Roche laboratories, oral preparations of Midazolam consisted of a mixtures of the IV solution and a palatable liquid diluents. The IV/syrpalta mixture prepared to yield a final drug concentration of 2 mg/kg, equivalent to the commercial syrup. Syrpalta is flavored syrup consisting of 83% sucrose, purified water, glycerin, 0.1% sodium benzoate, 0.001% benzalkonium chloride, 0.2% alcohol, and artificial coloring and flavors (pH 5). [23]

Midazolam syrup (versed) in the United States has pH-adjusted between 2.8 and 3.6 to ensure water solubility. In contrast the IV formulation in syrpalta has a pH of 4.5 to 5.0. Because of the pH of this mixture, the predominant form of the drug contacting the oral mucosa is the lipophilic and more readily absorbable form, probably permitting greater oral mucosal uptake. [23]

C) Pharmacokinetics:

1. Absorption:

Midazolam is rapidly absorbed from the gastrointestinal tract following oral administration. Parentral routes of administration result in higher bioavailability and rapid onset time. [24]

2. Distribution:

Midazolam has a volume of distribution (Vd) of 1-2.5 l/kg in normal healthy individuals. Obese patients have an increased Vd because of enhanced distribution to peripheral adipose tissues. Midazolam is extensively bound to plasma proteins primarily albumin with a free fraction representing only 4% of a given dose. The pharmacological effect of Midazolam ranges one to four hours. Midazolam has a short distribution half-life of several minutes because of fast tissue uptake. [25]

3. Metabolism:

Midazolam, like other benzodiazepines is biotransformed by hepatic microsomal oxidation followed by glucuronide conjugation. Initially, Midazolam is hydroxylated by cytochrome p450-3Aa to its primary metabolite, alpha hydroxyl-midazolam, and minimally to inactive metabolites. These metabolites are then excreted in urine as glucuronide conjugates. Alpha hydroxyl-midazolam binds to CNS benzodiazepine receptors and is pharmacologically active and has sedative properties equivalent to Midazolam. [26]

4) Excretion:

Midazolam has a short elimination half-life of 1.5-3.0 hours compared with more than 20 hours of diazepam. However, the pharmacological duration of action is generally only 60-120 minutes. Plasma clearance of Midazolam is 5.8-9 ml/min/kg in healthy individuals but is decreased in elderly individuals. Almost 90% of an orally administered dose of radiolabeled Midazolam is excreted within 24 hours. The major route of elimination is kidney, with less than 10% excreted in the feces within 5 days. Midazolam has been associated with accumulation and prolonged sedation in patients with renal dysfunction. [26]

D. Pharmacodynamics:

1. Mechanism of action:

Like mechanism of action of benzodiazepines via specific benzodiazepine receptors found at synapses through-out the central nervous system, but concentrated especially in the cortex and mid-brain. Benzodiazepine receptors are closely linked with GABA receptors, and appear to enhance the affinity of the GABA receptors for GABA. [25]

2. Pharmacological actions:

Cardiovascular system effects: on normal human CVS there is only relatively small effect in the form of slight depressant action, which becomes more significant on increasing dose, debilitated patients and hypovolemic patients. [30, 31]

Respiratory system: rapid injection and big bolus dose produce dose related respiratory depression. The tidal volume decreases but this is offset by an increase in the respiratory rate. Apnea may occur. The drug impairs the ventilator response to hypercapnia. [31, 32]

CNS effects:

- The cerebral oxygen consumption and cerebral blood flow are decreased in a dose-related manner.[23]
- Sedation and hypnosis.[25]
- Anxiolytic effect.[25]
- Muscle relaxant and anticonvulsant properties.[25]
- Anterograde amnesia: is a lack of recall of events occurring from the time of administration of a drug onwards. Midazolam affects memory process by impairing the ability to acquire new information.[25]

3. Adverse effects:

Benzodiazepines are remarkably safe drugs. But the most significant problem with Midazolam is respiratory depression.[23] Administration of higher oral Midazolam doses may result in higher incidence of side effects such as loss of balance and head control, blurred vision, dysphasia and increased level of sedation beyond minimal sedation. Careful titration of small doses combined with careful monitoring of the patient makes these adverse effects very rare. [24]

4. Drug antagonism:

Midazolam can be reversed with flumazenil which replaces benzodiazepines at the benzodiazepine receptor and interacts with the receptor in a concentration-dependent manner. [26]For the reversal of the sedative effects of benzodiazepines administered for conscious sedation in pediatric patients older than one year of age, the recommended initial dose is 0.01 mg/kg (up to 0.2 mg) administered intravenously over 15 seconds. In case the desired level of consciousness is not gained within 45 seconds, further injections of 0.01 mg/kg (up to 0.2 mg) can be administered and repeated at 60 seconds intervals where necessary up to a maximum of 4 additional times to achieve full consciousness and normal cardio respiratory function.[23]

Isoflurane

Isoflurane (2Chloro-2, 2, 2-trifluoroethyl difluoromethyl ether) halogenated ether used for inhalational anaesthesia. [32]

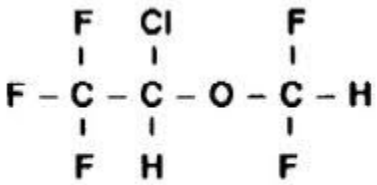

Figure (3): Isoflurane chemical structure

Isoflurane is always administered in conjunction with oxygen. Although its physical properties mean that anaesthesia can be induced rapidly, its pungency irritates respiratory system. It is usually used to maintain a state of general anaesthesia that has been induced with another drug. It vaporizes readily but is a liquid at room temperature. [32,33]

Isoflurane reduces pain sensitivity and relaxes muscles. The mechanism by which general anaesthesia produce anaesthesia state is not clearly understood but likely involves interaction with multiple receptor sites to interfere with synaptic transmission. Isoflurane binds to GABA receptors, glutamate receptors and glycine receptors and also inhibit conduction in activated k channels.

Glycine inhibition helps to inhibit motor function while bonding to glutamate receptors mimics the effects of NMDA. It activates Ca ATPase through increase in membrane fluidity and binds to a D subunit of ATP synthtase and NADH dehydrogenase. In addition a number of general anesthetics attenuate gap junction which could contribute to anaesthetic action. [33, 34, 35]

Pharmacokinetics

Pharmacokinetics of isoflurane are those of inhaled gases or volatile anesthetics for which blood concentration are related to alveolar concentration through the established partition coefficient and the distribution to tissue is also determined by solubility coefficient which are relatively constant under a wide variety of circumstances . Isoflurane shows very low solubility in blood and body tissues, much lower than for enflurane and halothane. Thus its partial pressure (concentration) in alveolar gas or arterial blood rises to 50% of the inspired partial pressure within 4to8 minutes of the start of its inhalation and to 60% within 15 minutes. This rate of rise is slightly faster than that obtained with enflurane (a structural isomer of isoflurane) and considerably faster than the more soluble halothane. Age significantly affects blood/gas partition coefficient for all anesthetics, the lower blood/gas partition coefficient in children explain in part the more rapid increase in alveolar anaesthetic partial pressure in this group.

Throughout maintenance of anaesthesia a high proportion of the isoflurane inspired is eliminated by the lungs. When administration is stopped and inspiratory concentration becomes zero the bulk of the remaining isoflurane is eliminated unchanged from the lungs. In keeping with its low solubility recovery from isoflurane anaesthesia in man is rapid. Biotransformation of isoflurane is significantly less than that of enflurane or halothane. Humans and animals biotransform a small fraction of isoflurane administered. In man (0.2%) administered is evident as recoverable metabolites. With approximately 50% of these excreted in the urine, the principal metabolite being trifluracetic acid. Enzyme

induction associated with preexisting drug therapy would not appear to be important factor in metabolism of isoflurane in man, mainly because overall metabolism of isoflurane is very low. [34-36]

Sevoflurane

Sevoflurane (2, 2, 2-trifluoro-1-[trifluoromethyl] ethyl fluoromethyl ether) also called fluoromethyl hexafluoroisopropyl ether, sweet smelling, non-flammable, highly fluorinated methyl isopropyl ether used for induction and maintenance of general anaesthesia. Together with desflurane, it is replacing isoflurane and halothane in modern anaesthesia. [37] After desflurane it is the volatile anaesthesia with the fastest onset and offset. [38,39] Though desflurane has the lowest blood/gas coefficient of the currently used volatile anaesthetic; sevoflurane is the preferred agent for mask induction due to its lesser irritation to mucus membrane [40-43]

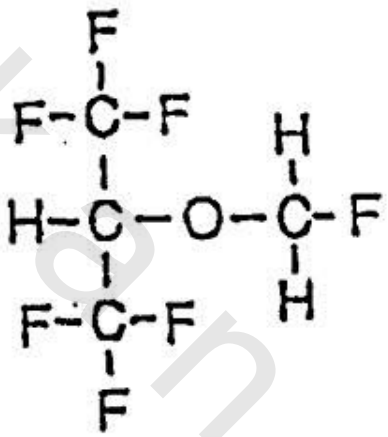

Figure (4): Sevoflurane chemical structure [32]

First reports of sevoflurane appeared in literature in 1971. The agent was developed by scientists at Baxter laboratories. It was introduced into clinical practice initially in Japan in 1990. The rights for sevoflurane in the US and other countries are held by AbbotLaboratories.

Sevoflurane forms at least 2 degradation products. Compound A and compound B.[44,46] on contact with soda lime in a rebreathing apparatus, which absorbs exhaled CO_2, especially at high temperatures and when soda lime is desiccated. Compound A has been shown to cause renal necrosis in rats. In humans direct histological evidence of renal toxicity has not been demonstrated, although there is dose related proteinuria, glycosuria and enzymuria.during low flow anaesthesia ,when the lower fresh gas flow leads to decreased flushing of the circuit and increase temperature of the soda lime, compound A may build up to clinically significant levels, although there have never been any reports of adverse events in humans. As a result sevoflurane is sometimes administered with a minimum fresh gas flow of 2 l/mmaking it relatively expensive choice for maintaining general anaesthesia. [45]