INTRODUCTION

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Surgery and anaesthesia induce considerable emotional stress upon children. Fears of operation, injections, physicians and peculiar operation theatre environment where the children are separated from their parents prior to anaesthesia invariably produce traumatic experiences in their tender mind. The consequyences of this stress may remain in the child's psyche long after the hospital experiences has passed, and it was first described by Dupuytren in 1834.[1]

Learning to cope with separation from a parent is necessary for a child's normal development. Separation experiences such as going to school facilitate normal psychological development and personality organization. Other separation experiences, such as perioperative separation, may precipitate confusion and anxiety. Between these two extremes, there are many separation experiences with varying degrees of psychological stress.[2]

In the first weeks of life, infants are able to discriminate among people, but will accept care and comfort from adults other than their parents. By 3 months of age, however infants begin to respond differently to familiar people and may even try to engage their attention. Separation anxiety usually begins at 7-8 months of age and peaks around 1 year of age. In part, separation anxiety represents the infant's acquisition of new cognitive abilities and object permanence. The intensity of separation anxiety declines with age, largely because of increasing in abilities and memory capacity. Frequently, however, the increase in abilities does not immunize toddlers and preschoolers against the stress and distress of separations.[3]

Preoperative anxiety stimulates the sympathetic, parasympathetic and endocrine system leading to an increase in heart rate, blood pressure and cardiac excitability. Maladaptive behavioral responses such as general anxiety, night time crying, enuresis and separation anxiety occur up to 44% of children two weeks after surgery and about 20% of these children will continue to demonstrate negative behaviors 6 months after surgery.[4]

Based on both behavioral and physiological responses, have indicated that induction of anaesthesia appears to be the most stressful procedure the child experiences during the perioperative period. Induction of anaethesia in children can be a challenge for the anaethetist. A stormy induction may increase the personality and behavioral changes from 17% to 57% and the incidence of nightmares, nocturnal enuresis and irritability is higher after a stormy induction of anaesthesia.[5]

Unpremedicated children frequently object inhalational and often feel that the use of needles is one of the most worrisome aspects of the hospital stay. Children aged two to six years are especially vulnerable to this problem, since their understanding is limited. Therefore, these children should be premedicated, in order to allow smooth induction, decrease anxiety and to prevent postoperative psychological and behavioral changes.[6]

Prenaesthetic medications in children are meant to releve anxiety, reduce the trauma associated with separation from their parents and facilitate induction of anaesthesia without prolonging the recovery period. [7]

Pediatric dentistry is that branch and specialty of dentistry concerned with providing primary and comprehensive preventive and therapeutic oral health diagnosis, care and consultative expertise for infants and children through adolescence, including those of all ages with special care needs [8-12]

Dental treatment rendered under general anesthesia (GA) includes amalgam restorations, extractions, stainless steel crowns, composite/glass ionomer restorations, formocresolpulpotomy, fissure sealants, strip crowns and pulpectomy. Amalgam restorations and extractions constituted the most frequent dental procedure performed on child dental patients under GA.[12]

History of paediatric sedation

Over the last few decades, there has been an increasing interest among pediatric health care providers (anesthesiologists or non-anesthesiologists) to relieve either pain or anxiety for children undergoing surgical procedures (diagnostic or therapeutic)until the beginning of the third millennium where studies showed that pain and anxiety are inseparable and should be treated together.[11]

In 1983, the first monitoring guidelines for sedation was written by Dr. Charles Cote and Dr. Theodore Striker (published in 1985) while working on behalf of the American Academy of Pediatrics (AAP) Section on Anesthesiology. This guideline was written in response to reports of three deaths in a single dental office and other concerns primarily involving dental sedation. Written with the cooperation of the American Academy of Pediatric Dentistry and the American Society of Anesthesiologists (ASA), the purpose of the guidelines was to develop a frame work from which improve safety could be developed for children requiring sedation to perform a required procedure. The concept of an independent observer whose only responsibility was to monitor the patient was introduced for deeply sedated pediatric patients. Advanced airway and resuscitation skills were encouraged but not required.[13]

In 1992, the Committee on Drugs of the AAP (primary author Dr. Cote) revised the 1985 guideline. This new iteration clearly stated that a patient could readily progress from one level of sedation to another and that the practitioner should be prepared to increase vigilance and monitoring as indicated. Pulse oximetry was recommended for all patients undergoing sedation. This new guideline also discouraged the practice of administering at home by parents a practice that was not infrequent in dental and radiological sedation at that time. Moreover, only three sedation levels were practically suitable for the paediatric age group: "conscious sedation" (AAP, 1992), "deep sedation" (AAP, 1992), and "general anaesthesia" (AAP, 1992).[14]

"Conscious sedation"[15] is a medically induced state of depressed consciousness during which there is a margin of safety wide enough to have a reasonable expectation that the patient:

a. Will be easily aroused.
b. Will maintain intact protective reflexes.
c. Will maintain airway independently.
d. Will have appropriate responses to stimulation, commands.

"Deep sedation" is a medically induced states of depressed consciousness during which it is reasonable to expect that the patient:

a. May not be easily aroused.
b. May developed partial or complete loss of protective reflexes.
c. May loose ability to maintain independent airway.
d. May be unable to respond appropriately to physical stimulation or verbal commands.

"General anaesthesia"[15] is a medically induced state of unconsciousness during which the patients:

a. Is not arousable.

b. Has complete loss of protective reflexes.
c. Has inability to maintain independent airway.
d. Has inability to respond to any stimulation or command.

In the 1998, the American College of Emergency Physicians (ACEP) published a state-of the-art policy statement for the management of acute procedural pain and anxiety in the emergency department, defining a new entity called "Procedural Sedation and Analgesia". PSA refers to "a technique of administering sedatives or dissociative agents with or without analgesics to induce a state that allows the patient to tolerate unpleasant procedure while maintaining cardiorespiratory function. Procedural sedation and analgesia intended to result in depressed level of produce a loss of protective airway reflexes". This definition is a significant improvement over the traditional AAP terminology; it accurately describes how sedation and analgesia should be practiced in the emergency room (ER).[16]

In September 2001, The American Academy of Pediatrics and the American pain Society jointly issued a policy on the assessment and management of acute pain in infants, children and adolescents. This statement provided a general definition of pediatric pain: "The concepts of pain and suffering go well beyond that of a simple sensory experience. It has emotional, cognitive and behavioral components as well as developmental, environmental and soico-cultural aspects." Furthermore, this statement emphasized the responsibility and the obligation of physicians to assess and treat acute pain in children.[17]

In 2001, the ACFP issued an updated policy statement on paediatric sedation, emphasizing that distraction. Sedation and analgesia should constitute a significant aspect of ER paediatric care. In 2002, an amendment to the (AAP, 1992) guideline was produced by the same committee on drugs of the AAP. It laminated the use of the term "conscious sedation" and clarified the fact that these guidelines apply to any location where children are sedated, including in or out of the hospital. The current guidelines use the terminology of minimal sedation, moderate sedation, deep sedation, and anaesthesia. This language is consistent with that used by the ASA and the Joint Commission Accreditation of Healthcare Organizations (JCAHO).[18]

"Minimal sedation" (Anxiolysis) is a drug-induced state during which patients respond normally to verbal commands. Although cognitive function and coordination may be impaired, ventilation and cardiovascular functions are unaffected.[19]

"Moderate sedation/analgesia" (conscious sedation) is a drug-induced depression of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained.[19]

"Deep sedation/analgesia" is a drug-induced depression of consciousness during which patients cannot be easily aroused but respond purposefully following repeated or painful stimulation. The ability to independently maintain ventilatory function may be impaired.

Patients may require assistance in maintaining a patient airway and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained.[19]

"General anaesthesia" is a drug-induced loss of consciousness during which patients are not arousable, even by painful stimulation. The ability to independently maintain ventilatory function is often impaired. Patients often require assistance in maintaining a patent airway and positive pressure ventilation may be required because of depressed

spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function may be impaired.[19]

Because sedation is continuum, it is not always possible to predict how an individual patient will respond. Hence, practioners intending to produce a given level of sedation should be able to rescue patients whose level of sedation becomes deeper than initially intended. Individuals administering "Moderate sedation/analgesia" Conscious sedation) should be able to rescue patient who enter a state of "Deep sedation/analgesia", while those administering "Deep sedation/analgesia" should be able to rescue patients who enter a state of general anaesthesia.[20]

Safety Issues in Pediatric Sedation

All providers of deep sedation (that is, everyone who sedates children for painful procedures) should be able to rescue patients from side effects of general anesthesia. Standards in terms of promoting safety and generally good sedation delivery should include, but not be limited to the following:[21]

1. Good skills for airway management.
2. Knowledge of disease entities that impact sedation and anesthesia.
3. Familiarity with sedation drugs, reversal drugs and rescue medications.
4. Optimal methods for monitoring ventilation as well as oxygenation.
5. All equipment required for emergency interventions (masks, airways, suction and ventilation bags) must be present for each sedation and regularly checked.
6. Sedation systems must have a quality improvement program that examines its own outcomes on a continuing basis.

An appropriate pre-sedation assessment reduces complications of sedation. A focused history-taking and physical examination should precede sedation. The history should include underlying medical problems, medication use, medication allergies, previous surgery or sedation, any adverse reaction to sedation in the past, last oral intake and events leading to the procedure. The physical examination should be directed to the upper airway and full cardiopulmonary assessment. According to the guidelines of the American Society of Anesthesiologists (ASA), only children classified as ASA I or ASA II should be included.[22]

The American Society of Anesthesiologists (ASA) recommends nothing-by-mouth (NPO) guidelines for elective procedures to include the following:[23]

a. No oral liquids up to 2 hours before procedures in children younger than 2 years and 3 hours if older than 3 years.
b. Avoidance of milk or solids for 8 hours prior to procedures is preferred. This recommendation persists despite literature showing that maximal gastric emptying occurs 3-4 hours post-prandially.
c. In an emergency, if practicable, delay sedation or use the lightest level of sedation possible. Position airway equipment at the bedside.

The recommended ASA guidelines for duration of fasting before elective procedures therefore vary with age. However, the guidelines acknowledge the fact that there are insufficient data to test the assumption that pre-procedure fasting results in a decreased incidence of adverse outcomes. The risks and benefits must be assessed for each patient by

balancing the potential for vomiting and aspiration with the timing and urgency of the procedure and the depth of the sedation required.[24]

Preoperative anxiety

Anxiety is normal healthy reaction and is the expected response in a strange situation. Anaesthesia and operation are not familiar activities and fear reactions could result from such experience for most people and so we might predict these anxieties. For every situation there is an optimal level of anxiety and it is the role of the anaesthesiologist to find the correct way to talk to this patient to gain his confidence, manage his anxiety and adjust it to an appropriate level. Anxiety is a universal human experience characterized by fearful anticipation of an event in the future. It is a normal feature of life comprising stresses necessary to alert the organism to fend for itself or to delineate itself. All people are subjected to a stresses, but the normal person is equipped for these. He meets and deals with them completely. Herediatary factors are important as they predispose to anxiety state. Anxiety may be acute of chronic.[25]

Physical manifestation of acute neurosis

Sweating, pallor, tachycardia, raised blood pressure, rapid and deep respiration, diarrhea and frequency are common in acute neurosis which indicate some parasympathetic activity.[25]

Mental manifestation of acute neurosis

Fear, tension and apprehension lead to lack of concentration and insomnia, particularly early insomnia. The physical basis of these mental manifestations is an increased autonomic nervous system response, especially involved sympathetic system.[25]

Some people respond abnormally to stress in an extreme form of anxiety which includes:[26]

a. The panic state.
b. The terror state.
c. The anxiety exhaustion syndrome

In the chronic stage of anxiety there is marked stimulation of the hypothalamus which is the center of emotion and at the same time the center of the autonomic nervous system. At the chronic stage of anxiety the symptoms vary considerably and in one patient will show several, but not all of the following feature:[26]

a. Sleep disturbance.
b. Weakness and motor changes.
c. Irritability.
d. Vasornotor palpitation, flushing, urticaria, eczema and vertigo
e. Subjective sensation: inabilityto concentrate and work, feeling of unreality, headache, hunger pain and feeling of choking..
f. Systemic changes.

    1. Cardiovascular system showed tachycardia, throbbing of the vessels and fainting feeling.
    2. Respiratory system showed precipitation of bronchial asthma.
    3. Skin showed eczema and urticaria.

Beside the above feature of anxiety, the effect of preoperative anxiety extend to the operative anxiety which leading to difficulty in getting a vein, impede induction of anaesthesia, past to postoperative period leading to more need for pain medications and longer stay in the hospital.[26]

Factors that affect preoperative anxiety[27]

1. Sex: female tend to be more apprehensive.
2. Age: is highly important associated with immaturity on the one hand and with advanced age on the other.
3. Worries about having to leave home and disturb the domestic arrangements.
4. Fears about general health, worry about the nature of the operation.
5. Fears of anaesthesia itself.
6. Fears of post operative discomfort.

Unfortunately, not all these anxieties could be relieved before the operation.

Management of preoperative anxiety[28]

Preparing the paediatric patients for their operative room experience can be complex process because of the many individuals involved.

The preoperative interventions directed towards reduction of anxiety can be grouped into psychological and pharmacological methods. Preparation begins before patients have seen an anaesthetist because they will learn of their impending surgery from the surgeon . Surgical colleagues and support staff can help to ease parents' anxieties by assuring them that their child will receive the best anaesthetic care possible. The uses of preoperative hospital tours, educational videos and pamphlets have been demonstratedto have value in reducing patient and parents' anxieties.

The preoperative visit anaesthetist

Any patient expects from his doctor the skill of dealing with his physical disability and the understanding of the emotional reaction to his disability. If doctors offer both skill and understanding, fears and anxiety can be allied. The importance of the preoperative visit by an anaesthetist cannot be over emphasized, so anaesthetist may study the patients physical problems, but also that he may give his psychological support for his coming operation. The anaesthetist must find a correct way to talk to his patient to gain his confidence and to find out the child fear urmoticeably.[29]

It is important to understand that the entire family is undergoing anaesthesia and surgery in the sense that anxiety felt by the parents will be transmitted to the child. Children who observe upset parents will become upset because they realize that something terrible is going to happen to them. The anaesthetist should also determine if having a parent accompany the child to operation room would be of benefit during induction in these days of increased parent awareness, being present for induction may in some cases be of equal support to the parents and the child. For some children having parent present completely eliminate the need for premedication. Some parents are upset by this process and if a parent to be present, it is vital to prepare the parent for what they will observe so that they are less likely to be frightened.[29]

Premedication[30]

Premedication is an aid, not substitute for sympathy and reassurance. The ideal premedication for ambulatory anaesthesia in children, one to six years of age, should possess the following attributes:

1. An acceptable, atraumatic route of administration.
2. Rapid and reliable onset.
3. Minimal side effects.
4. Rapid elimination.

Preanaesthetic medications are administered mainly to achieve the following[31]

1. To lessen the preoperative anxiety, fear, emotional stress and tension.
2. To make induction and maintenance of anaesthesia more easy.
3. To prevent the undesirable side effects of the anaesthetics on various organs.

Factors affecting the dose of the Preanaesthetic drugs[32]

1. Age and weight

The effect of drug in general and of sedatives in particular is closely related to the metabolic activity and general excitability of the patient. The dose per unit weight is therefore scaled down with increasing age. The metabolism of old people is low; in the young it is high. At birth the dose per unit for a particular effect is greater than that for the adults. The dose weight ratio rises until between the ages of 6-10 years, it is about 25% more than the adult ratio. It is then gradually drops until the age of 20 years, the individual is considered an adult, and needs the average or usual dose.

2. Temperature

Febrile patients need slightly increased doses to show the same effect because of the rise in the metabolism. Increase the temperature by 1°C leading to increase the basal metabolic rate by 8.3%.

3. Pain

Pain is an indication for analgesics like opioids rather than hypnotics like barbiturates. The administration of a barbiturate to a patient in pain may lead to uninhibited reflex reaction to pain in the form of restlessness that may be so marked to induce the risk of injury.

4. Physical state

Patients vary in their general state of health. If a normal dose is given to an anemic patient, exaggerated effect may follow and the patient perhaps needs resuscitation.

5. Emotion

The ratio between the dose of thesedative drugs and emotional stress need not emphasis.

6. Route of administration[33]

Route of administration of premedication in children

1. **Intravenous route (IV)**

IV premedication and induction is used generally in patient requiring rapid sequence induction or those established IV access.

2. **Intramuscular route (IM)**

IM administration is painful to administer, can be threatening to the child, a sterile abscess may form and often the major adverse experience the child remembers is the shot they receive.

Though the drug is well absorbed intramuscularly and intravenously, but these routes remain far from ideal for young children, as injections are by themselves fear evoking. Therefore, many institutions have moved away from IV and IM premedication.

3. **Rectal route**

Rectal administration is reliable & painless and is advocated in very young children up to 2 years of age, but children as well as the doctors may find the procedure distressing. The major concern with rectal drug administration is that there is irregular absorption with some children having very rapid uptake and other having delayed drug uptake. An additional factor is that some drugs undergo first pass metabolism if administered high in the rectum where as if the drug is administered low in the rectum.

In general this route of premedication is appropriate for children still in diapers but is not very well accepted by an older patients.

4. **Transdermal drug administration**

A number of drugs may be administered transdermally. Transdermal drug absorptioncan significantly alter drug kinetics and depends on a variety of factors including the following:

- Site of application.
- Thickness and integrity of the stratum corneumepidermidis.
- Size of the molecule.
- Permeability of the membrane of thetransdermal drug delivery system.
- State of skin hydration.
- pH of the drug.
- Drug metabolism by skin flora.
- Lipid solubility.
- Depot of drug in skin.
- Alteration of blood flow in the skin by additives and body temperature.

The potential for toxic effects of the drug and difficulty in limiting drug uptake are major considerations for nearly all transdermal delivery systems, especially in children because skin thickness and blood flow in the skin vary with age. In some situations this may be an advantage, while in others systemic toxicity may result.. The practitioner must understand the clinical implications of these factors when prescribing a drug to be administered by the transdermal route.

5. **Oral route**

The oral route is widely used and provides effective sedation. However, some authorities have expressed concern about the wide bioavailability when given by this route, ranging from l8% to 44% with an appreciable first pass effect. Sublingual route is effective

but has poor compliance. Oral and sublingual routes are found to be effective through various studies in the world. A drug which has a bitter taste when mixed in a suitable flavoring agent becomes well tolerated orally. The disadvantages of oral route are a relatively larger dose requirement, which is due to the first pass metabolism of the drug in the liver and a delayed peak effect i.e. about 30 minutes. The sublingual route has an advantage of avoiding first pass metabolism and showing a rapid systemic absorption directly from the mucosa. Unfortunately, to be effective, it has to be kept under the tongue for about 30 seconds, which may be difficult to achieve in preschool children who have not yet developed the ability to understand complicated instructions. In 1993 showed that almost 62 percent of pre-school children given a flavored midazolam prcparation with an instruction of keeping the drug under tongue for 30 seconds, showed an early swallow, being able to retain it for an average of 17 seconds i.e. approximately half the needed time duration.

6. Trans-mucosal route

An alternative route of drug administration is the trans-mucosal route, in which the drug is administered orally but in small increments to prolong contact with oral mucosa. This route has been widely used for administration of drugs such as fentanyl.

The amount of drug absorbed depends on the following factors:

- Drug concentration.
- Vehicle of drug delivery.
- Mucosal contact time.
- Venous drainage of the mucosal tissues.
- Degree of the drug's ionization and the pH of the absorption site.
- Size of the drug molecule.
- Relative lipid solubility.

7. Intranasal route (IN)

The IN route has become used since 1988 and has the advantage of rapid absorption directly into the systemic circulation with no first pass effect and bioavailability of 55 to 83%. The nasopharyngeal mucosal surface is relatively large and well vascularized, allowing for a rapid absorption of the drug.

The nasal mucosa has been used for the administration of sedatives and potent narcotics, which generally results in a rapid systemic response.

Although nasal Preanaesthetic medications can cause irritation to the nasal mucosa and patient crying, its rapid and reliable onset of action, avoidance of painful injections, and ease of administration have made it a convenient way to premedicate children.

Ketamine hydrochloride

Ketamine molecule (2-0-chiorophenyl 2-methylamino-cycihexanone hydrochloride). chemically related to phencyclidine and cyclohexamine.[34]

Physicochemical characteristics

Source

Ketamine is synthetic phencyclidine derivative.[34]

Molecu1ar weight

Ketamine is a white crystalline solid with a molecular weight of 238, and melting point of 259°C. It is soluble at room temperature. It is supplied as an acidic solution (pH of 3.5- .5), available in 10, 50, 100 rng per ml/strengths suitable for IV or IM injections. It contains 1:100 000 benzethoniurn chloride as preservative.[35]

Pharmacokinetic[36]

Hepatic Primary metabolic pathway involves hepatic N- dernethylation via the cytochrome P450 system to form norketarnine; this metabolite is subsequently hydroxylated and conjugated to water soluble compounds.. Only 16% of ketarnine is bioavailable orally as opposed to 93% IM or IV. It has also been shown that oral ketarnine doses equivalent to IM doses produce peak plasma concentration only in 1/5th as high as IM delivered and the time to reach peak plasma concentration is longer. Time to maximum sedation is approximately 20 to 25 minutes with patients blinking, staring, losing their lid reflexes, demonstrating nystagmus and appearing dissociated. However, the plasma concentration of norketamine is twice as high after oral administration of ketamine. This increased amount of norketamine with oral administration may account for part of the sedative effect observed and possibly the reduced incidence of unwanted side effects with oral administration.

The pattern of biodisposition of ketarnine is analogous to that of the short acting barbiturate such as thiopental, which resemble in term of its onset of action, relatively short duration of hypnotic effects and is high lipid solubility.

Initially, ketamine is distributed to the highly perfused tissues including the brain, to achieve levels four to five times that of the risk tissue to less perfused tissues. Repeated administration of ketarnine increases the activity of hepatie drug metabolizing enzymes including those responsible for the metabolism of ketamine itself. Termination of anaesthetic effects may be caused by redistribution from the brain to other tissues.

Distribution[37]

Approximately 10—17 minutes.

Elimination[37]

Approximately 2.5-3 hours. Approximately 1-2 hours in children, suggesting more rapid metabolism or elimination in this population.

Time to induction of anaesthesia[37]

- **Intravenous** (following a dose of 1 to 2 mg per kg of body weight)Sensation of dissociation: 15 to 30 seconds.Anaesthesia: 30 to 60 seconds.
- **Intramuscular** (following a dose of 9 to 13 mg/kg):Anaesthesia: 3 to 4 minutes.

Duration of action [37]

- **Intravenous** (following a dose of 2 mg/kg):5 to 10 minutes.
- **Intramuscular** (following a dose of 9 to 13 mg/kg):12 to 25 minutes.

Elimination [37]

Renal, 9% as hydroxylated and conjugated metabolites; about 4% as unchanged ketarnine or as norketamine. Fecal elimination occurs up to 5%.

Pharmacological action of ketamine[37]

Ketamine is a rapid acting non-barbiturate parental general anaesthetic. It is one of the dissociative general anaesthetics. It has been described as having cataleptic, analgesic and anaesthetic action but without hypnotic properties.

Mechanism of action/Effect[37]

The precise mechanism of action is unknown. Ketarnine has been shown to block afferent impulses associated with the affective-emotional component of pain perception within the medial medullary reticular formation, to suppress spinal cord activity, and to interact with several transmitter systems in the central nervous system (CNS) Ketamine blocks the N -methyl-D-aspartate (NMDA) glutamate receptor by a dual mechanism, blocking both the closed channel from the aqueous phase and the closed channel from the membrane phase. Ketarnine binds stereo specifically to opiate receptors, possibly competing with narcotic analgesics and endogenous morphine like compounds for C.N.S. and spinal cord receptor. Ketamine has been claimed to produce insufficient protection against increased pain but effective against pain involving extremities and skeleton somatoanalgesia, result in visceral operation. Ketamine also produce anterograde amnesia.

Otheractions/effects [38]

Cerebrovascular

Ketamine increases intracranial cerebrospinal fluid pressure.

Cardiovascular

Ketamine may transiently increase blood pressure and heart rate. The increase in blood pressure may be up to 50% over the preanaesthetic values, but usually decreases to preanaesthetic values within 15 minutes of initial administration.

Respiratory

Ketamine does not decrease the respiratory response to hypercapnia. Ketamine relaxes bronchial smooth muscle. Despite the usual lack of respiratory depressant effects, apnea can occur, especially with rapid injection of ketarnine.

Skeletal muscles

Ketamine frequently produce an increase in skeletal muscle tone, especially of extremities and masseter muscles.

Ocular effects

Slight elevation of intra-ocular pressure, about 2-3 cmHg this elevation is transient and of no significance. Nystagmus is a common finding.

Drug interactions and/or related problems[38]

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance:

1. Halogenated hydrocarbon inhalational anaesthetics may prolong the elimination half - life of ketamine; recovery from anaesthesia may be prolonged following concurrent use (combined administration of halothane and ketamine has resulted in clinically significant decreases in blood pressure, heart rate, and cardiac output).
2. Barbiturates, Narcotics or benzodiazepines (concurrent use with ketamine may prolong recovery time).
3. Thyroid hormones (ketamine should be administered with caution to patients receiving thyroid hormones because of the increased risk of hypertension and tachycardia).

Side/Adverse Effects[38]

The following side/adverse effects have been selected on the basis of their potential clinical significance.

A. Those indicating need for medical attention:

1. Incidence more frequent
   a. Increased blood pressuremay reach hypertensive levels.
   b. Tachycardia.
   c. Tonic and clonic muscle movements may resemble seizures.
   d. tremor.
   e. vocalization.
2. Incidence less frequent
   a. Bradycardia.
   b. Hypotension.
   c. Respiratory depression, may lead to apnea.
   d. Vomiting.
3. Incidence rare
   a. Cardiac arrhythmias.
   b. Laryngeal spasm or other forms of airway obstruction.

B. Those indicating need for medical attention only if they continue or are bothersome.

1. Incidence is more frequent in patients between 15 and 45 years of age and less frequent in other age gioups.
   a. Emergence reaction: (alterations in mood or body image; delirium; dissociative or floating sensations).
   b. Visual hallucinations.
   c. Vivid dreams or illusions.

Note: although vivid dreams and/or hallucinationsusually disappear uponwakening, some patients may experience flashbacks several weeks postoperatively.

2. Incidence less frequent or rare.
    a. Double vision.
    b. Loss of appetite.
    c. Nausea with or without vomiting.
    d. Nystagmus (wandering or back-and-forth eye movements).
    e. Pain at injection site.
    f. Reddened skin or skin rash.

Medical considerations/Contraindications[39]

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance.

Except under special circumstances, this medication should not be used when the following medical problems exist:

- Severe cardiovascular disease.
- Severe or poorly controlled Hypertension.
- Recent history of myocardial infarction.
- History of stroke.
- Cerebral trauma.
- Intracerebral mass or hemorrhage.
- Alcohol or drug abuse or addiction (or history of).
- Acute alcohol intoxication.
- Tachyarrhythmia (may be exacerbated).
- Eye injury, open globe.
- Increased cerebrospinal fluid (CSF) pressure (ketamine may further elevate CSF pressure).
- Increased intraocular pressure (ketamine may further elevate intraocular pressure).
- Psychiatric disorders such as schizophrenia or acute psychosis (ketamine can cause anxiety, disorientation, dysphoria, and hallucinations).
- Hypersensitivity to ketamine.
- Thyrotoxic states (increased risk of hypertension and tachycardia).

Usual adult and adolescent dose

General anaesthesia[40]

Induction

- Intravenous: 1 to 4.5 mg per kg of body weight, administered as a single dose.
- Intramuscular: 6.5 to 13 mg per kg of body weight.

Maintenance

- Intravenous infusion, 100 to 500 meg (0.1 to 0.5 rug) per kg of body weight.

Local anaesthetic adjunct[40]

Intravenous: 5 to 30 mg, prior to administration of the local anaesthetic. The dose may be repeated if necessary.

Sedation and analgesia[41]

Intravenous: 200 to 750 mcg (0.2 to 0.75 rng) per kg of body weight administered over 2 to 3minutes initially, followed by 5 to 20 meg (0.005 to 0.02 ing) per kg of body weight per minute as a continuous intravenous infusion.

Intramuscular: 2 to 4 mg per kg of body weight initially, followed by 5 to 20 meg (0.005 to 0.02 mg) per kg of body weight per minute as a continuous intravenous infusion.

Usual pediatric dose[42]

Anaesthetic (general)

Neonates through children 16 years of age:

Induction

- Intravenous: 2 mg per kg of body weight, and titrated to individual response as necessary.
- Intramuscular: 4 to 12 mg per kg of body weight.

Sedation and premedication for procedures in paediatric patients[43]

Infants 4 months of age through children 15 years of age:

- Intravenous: 1 to 2 rng per kg of body weight. Dose may be titrated to the individual response of the patient.
- Intramuscular: 4 to 5 mg per kg of body weight. Dose may be titrated to the individual response of the patient.
- Intranasal: 4 to 6 mg per kg of body weight.
- Oral: 5 to l0 mg per kg body weight.

Dexmedetomidine

History

Dexmedetomidine was approved by food and drug administration at the end of 1999 for use in humans as a short term medication (<24h) for analgesia and sedation in the intensive care unit (ICU). Its unique proparties render it suitable for sedation and analgesia during the whole perioperative period.

Physiochemical characteristics

Medetomidine is a highly selective alpha2-adrenergic agonist. Dexmedetomidine is its specific stereoisomer which is available as a parental formulation.

Description

Dexmedetomidine hydrochloride is a compound chemically described as [1-(2,3dimethylphenyl)ethyl]-1H-imidazole monohydrochloride and has a molecular weight of 236.7 and the empirical formula is C13H16N2.HCI.

Dexmedetomidine hydrochloride is a white or almost white powder, freely soluble in mater and its pKa is 7.1. dexmedetomidine is supplied a clear,colorless, isotonic solution with a pH of 4.5 to 7.0 . Each 1 ml of dexmedtomidine contains 118 mcg of dexmedetmine HCI (equivalent to 100 mcg dexmedetomidine base) and 9 mg of sodium chloride in water. The solution is preservative free and contain no additive or chemical stabilizers.

Metabolism and Pharmacokinetics[47]

It is believed that the drug is the first hydroxylated and subsequently undergoes either dehydrogenation to form a carboxylic acid derivative or glucuronidation. Metabolites are excreted in urine (about 95%) and in the feces (4%).[48]

It is unknown wether they posses intrinsic activity.it may be necessary to decrease the dose in patients with hepatic fauilre,since they will have lower rates of metabolism of the active drug .[49]

Dexmedetomidine is 94 percent protein bound with negligible protein binding displacmenet by fentanyl,ketorolac, theophylline, digoxin and lidocaine,drugs commonly used during anesthesia and in the icu.[50]

Dexmedetomidine has profound effects on the cardiovascular parameters and thus appears to affect its own pharmacokinetics. At high doses, there is marked vasoconstriction, which probably reduces the drug"s volume of distribution. Thus, in essence, dexmedetomidine displays nonlinear pharmacokinetics. Because it is likely that this agent will not only be administered within a narrow therapeutic range of 0.5 to 1.0 ng/ml, it is preferable to describe the pharmacokinetic paramters within this dosage range. These pharmacokinetic paramaters appear to be unaltered by age or weight. The elimination half life of dexmedetomidine is 2 to 3 hours, with a context sensitive half-time ranging from 4 minutes after a 10 minute infusion to 250 minutes following an 8-hours infusion. An intramuscular injection of 2mcg/kg of Dexmedetomidine into the deltoid muscle had a bioavalbility of 73 % with a time peak comcentration of 13 minutes and resulted in a peak plasma concentration of 0.8ng/ml. Injection into the gluteus muscle however,results in a much longer time to peak effect of approximately 90 minutes.[51]

Pharmacodynamics

The mechanism of action is unique and differs from those of currently used sedative agents. Alpha2 receptors are found in the peripheral and central nervous system,platlets,and many other organs, including the liver, pancreas, kidney and eye. Activation of the receptors in the brain and spinal cord inhibits neuronal firing, causing hypotension, bradycardia, sedation and analgesia. The response to activation of the recopters in other areas include decreased salivation, decreasd secretion, and decreased bowel motility in the gastroinitestinal tract, contraction of vascular and other smooth muscle, inhibition of renin release, increased glomerular filtration and increased secretion of sodium and water in the kidney, decreased intra ocular pressure and decreased insulin release from the pancrease.[52]

In general, presynaptic activation of the alpha2 adrenoceptors inhibits the release of norepinephreine, terminating the propagation of pain signals. Postsynaptic activation of alpha2 adrenoceptors in central nervous system (CNS) inhibits sympathetic activity and thus can decrease blood pressure and heart rate. Combined, these effects can produce analgesia, sedation and anxiolysis. Dexmedetomidine combines all these effects, thus avoiding some of the side effects of multi-agent therapies. The mechanism of the analgesicactions of alpha2 agonist have not been fully alucidated the hypnotic and sedative effect of alpha 2 adrenceptor activation have been attributaed to the site locus soerules in the CNS.[52]

Effect on the central nervous system

The alpha 2 agonist produce their sedative hypnotic effect by an action on the alpha 2 receptors in the locouscoeruleus and an analgesic action both at the alpha 2 receptors within the locus coeruleus and the spinal cord. Like other adrenergic receptors, they demonstrate tolerance following prolonged administration of dexmedetomidine.(53)

Effect on the cardiovascular system

The basic effect of alpha 2 agonist on the cardiovascular system are decreased heart rate, decreased systemic vascular resistance, and indirectly decreased myocardial contractility, cardiac output and systemic blood pressure . By developing highly selective alpa2agonist, it has been hoped to deacrease some of these adverse cardiovascular effects and to maximize the desirable hypnotic-analgesic properties. Thus dexmedetomidine is the most selective that is likely to be used in clinical practice .(53)

The hemodynamics effects of dexmedetomidine in humans have shown a biphasic response . An acute of intravenous injection resulted in an initial increase in blood pressure and decrease in heart rate 5 minutes after injection . this initial increase in blood pressure is probably due to the effect on peripheral receptors heart rate returned to base line by 15 minutes, and blood preasure gradually drifted down to approximatly 15 % below baseline by one hour.(54)

Following an intramuscular injection the initial increase in blood pressure was not seen and both heart rate and blood pressure remained within 10% of baseline.(55)

Transient hypertension has been reported with the administration of the loading dose due to initial vasoconstriction caused by stimulation of peripheral postsynaptic $alpha_{2B}$-adrenergic receptors.(56)

Dexmedetomidine demonstrated some beneficial effects on the ischemic heart through decreased oxygen consumption and redistrutaion of coronary flow from no ischemic zones to ischemic zones following acute brief occlusion.(57)

Clinical applications

Premedication

As a premidicant,dexmedetomidine, at intravenous doses of 0.33 to 0.67 mcg/kg given 10 minutes prior to surgery, appears beneficial while minimizing the cardiovascular side effects of hypotension and bradycardia within this dosage range it reduces aneastheticrequriments by 30% and the requirments of volatile anesthetics by 25 % .(58)

Maintance of anesthesia

It is also been used as amaintance infusion as apossiably useful adjvant during anesthesia.(58)

Side effects and precautions

Bradicardia, hypotension is the most common and poteniatlly serious side effect which was found self limiting and can be controlled acutly by simple IV fluid administration.

Dry mouth is a frequently reported side effect.

Clinical experience in children

Preliminary Experience

Initial reports of the use of dexmedetomidine as a sedative in the pediatric population were published in two case series from the same institution. The first, published in 2002, described experience with dexmedetomidine in two children during mechanical ventilation, in one child during surgery, and in one other for procedural sedation. Infusion rates ranged from 0.25 to 0.7 mcg/kg/hr.[59] Although dexmedetomidine produced mild decreases in heart rate and blood pressure in three patients, no intervention was required. Three patients achieved adequate sedation, but an 11-year-old boy undergoing endoscopy required the addition of midazolam and ketamine before his procedure could be performed. Their second paper described dexmedetomidine use in five additional children. Three were given an IV loading dose of 0.5 mcg/kg over 10 minutes followed by an infusion of 0.25 mcg/kg/hr, titrated to response. The two remaining patients were given a single 0.5 mcg/kg IV bolus dose. All of the patients achieved the desired level of sedation. As in their initial case series, the children tolerated dexmedetomidine without significant adverse effects. Based on the successful use of dexmedetomidine in these two case series, the authors concluded that this agent deserved further study as a sedative for children.[60]