7. Specific Techniques

The pharmacopoeia of agents used for sedation and analgesia has evolved from a limited number of long acting agents (diazepam, trimeprazine, pethidine, morphine) with limited routes of administration to a wide range of shorter acting agents with many routes of administration (topical, local, transmucosal, oral, intranasal, rectal, intra-muscular, intravenous and inhalational).

A sedation analgesia plan should be individualised according to the child needs and may often be influenced by the anxiety of the family or even the practitioner.

Ideally short acting agents, which have specific antagonists, should be used because they can be titrated to effect. Invariably these agents have the smallest margin of safety and the risk of complications is high in inexperienced hands. Their short duration and the ability to antagonise their action of the drug can be life saving. Rapid reversal in itself is not without risk and should not be used routinely.

Many drugs used for sedation and analgesia are not approved for use in children. The classes of drugs listed below have been used effectively – either alone or in combination. Individual practitioners should gain experience with a particular agent or agents so that they become familiar with the particular nuances of the drug alone or in combination with other drugs.

Psychological techniques to allay anxiety should not be forgotten. Time spent gently reassuring the child, allowing parents to be present, cuddling, the use of warm blankets and even hypnosis have been shown to be useful adjuncts to the sedation plan.

7.1 Anxiolytics and sedatives

7.1.1 Midazolam – a short acting imidazo-benzodiazepine – is commonly used for sedation in children and has essentially replaced the longer acting benzodiazepine diazepam. Benzodiazepines have anxiolytic, anti-convulsant, sedative, muscle relaxant and amnesic properties.

| Table I: Midazolam synopsis |
|--------------------------------|
| Administration | Oral | 0.5mg kg (0.25-0.75mg kg) |
|                 | Sublingual | 0.25 – 0.3mg kg |
|                 | Nasal | 0.2 – 0.3mg kg |
|                 | Intravenous | 0.05 – 0.15mg/kg (titrate to effect) |
|                 | Intramuscular | 0.05 – 0.15mg/kg (painful and not recommended) |
|                 | Rectal | 0.5 – 0.75mg/kg |
| Time to peak effect | Oral | 10 – 30 min |
|                     | Sublingual | 10 – 15 min |
|                     | Nasal | 10 – 15 min |
|                     | Intravenous | 3 – 5 min |
|                     | Rectal | 10 – 20 min |
| Duration of action | Intravenous | 20 – 60 min (dose related) |
|                     | Oral and rectal | 60 min (dose related) |
| Adverse reactions | Respiratory depression; Ataxia, Diplopia; Paradoxical excitation; Hypotension; Nasal burning, bitter after taste | Dose related; common with opiates - reduce dose by 25-30% |
|                   | | Rapid administration, especially in hypovolaemia, neonates |
|                   | | If used intranasally |
| Drug interactions | Opiates, barbiturates etc; CNS depressants; Erythromycin; Ca²⁺ channel blockers; Protease inhibitors | Respiratory depression; apnoea; prolonged sedation |
|                   | | Prolongs recovery |
|                   | | Delay metabolism (inhibit cytochrome p450) |
|                   | | Delay metabolism (inhibit cytochrome p450) |
|                   | | Inhibit cytochrome p450 enzyme; titrate slowly in HIV patients on antiretrovirals |
| Special concerns | Decrease dose in high risk/debilitated patients; Risk in upper airway obstruction | |
| Antagonist | Flumazenil | 10ug/kg ivi given slowly over 15 seconds - repeat every 2-3 mins - up to max 1mg kg |
Midazolam exerts its effects by interacting with gamma-aminobutyric acid (GABA) receptors in the central nervous system. The sedated child usually becomes compliant but does not lose consciousness (when recommended doses are used).

Antegrade amnesia is common, but not universal, and is an advantage seen in most children. Mild respiratory depression and upper airway obstruction is dose related. When used in combination with opiates, midazolam can produce a "superadditive effect" (i.e. the total effect of the combination is greater than the sum of the anticipated effect of the individual drugs). Midazolam should therefore be used with caution in compromised children or those with upper airway obstruction (tonsil hypertrophy for example).

Midazolam provides no analgesia. Children frequently move in response to stimuli and supplementing another agent maybe necessary if the child must not move for the procedure to be accomplished.

Although many children initially act disinhibited following small doses, some may have a true paradoxical response and become more agitated with higher doses. In this event it is wiser to switch to an alternative sedative since increasing the dose may lead to severe agitation followed by unconsciousness and respiratory compromise. Diplopia is the most distressing effect for the child.

Midazolam can be given intravenously, intranasally, sublingually, orally or rectally. The oral route has become increasingly popular and is well tolerated. The cherry flavoured syrup is currently not available in South Africa but the intravenous preparation can be mixed with more palatable juices (apple, orange, grape) or drinks (coke, fanta, lemonade) or even analgesics (panade, stopayne, ponstan) in order to disguise the bitter aftertaste. The volume (1ml/kg has been suggested as a useful starting point) should be reduced to the smallest possible volume, to administer the drug. The bioavailability of midazolam used in this way has not been determined scientifically but is clinically effective. Fifty percent is metabolised by the hepatic "first pass" effect and thus the route of administration will determine the effect.

Rectal administration is also usually well tolerated in children who have not been toilet trained (<1 year), but absorption may be irregular. Nasal administration causes burning and leaves a bitter after taste for up to two days so should be avoided.

The effects of midazolam can be reversed with the antagonist flumazenil.

7.1.2 Flumazenil - a specific benzodiazepine antagonist and will rapidly reverse the sedative and respiratory effects of benzodiazepines by competitive inhibition. Caution should be exercised in those patients who are taking benzodiazepines for seizure or behavioural disorders because those symptoms may recur if flumazenil is given.

10ug/kg flumazenil should given slowly iv every 2-3mins until the desired effect is achieved. The onset time is approximately 1-2 minutes and lasts approximately 1 hour. Because of the disparity in the half lives of the two drugs the risk of resedation is real. The child must be carefully monitored for at least 2 hours because a repeat dose may be necessary. Flumazenil should not be used routinely but should be reserved for those children with respiratory depression. Flumazenil will not reverse the respiratory depressant effects of the opiates and should never be used for that purpose.

7.1.3 Trimeprazine (Vallergan) - a long acting phenothiazine - has been used for many years. It is available in two preparations 1.5mg/ml and 6mg/ml (forte) which contain alcohol and preservatives.

Trimeprazine can only be given orally and absorption is erratic. The onset time is thus variable and slow (60-90min). The recommended dose is 1-2mg/kg. Higher doses are associated with an increased risk of toxicity. Trimeprazine has a prolonged duration of action and therefore is inappropriate in an outpatient setting particularly when mixed in a "lytic cocktail".

Side effects include dry mouth, sweating, tachycardia (anti-cholinergic effects) fever, rash, convulsions and coma. Disorientation and occasional paradoxical excitement has been described. Trimeprazine hyperactivity is no longer a factor since the preservative is no longer used.

7.1.4 Chloral hydrate is one of the oldest sedative agents but is no longer freely available in this country. Oral chloral hydrate has a well established safety profile particularly in children under 3 years, but is unreliable in older children. Despite this safe record it can still cause airway obstruction in susceptible individuals and deaths have been recorded when used on its own or when used in combination with other respiratory depressants. It has no analgesic properties.

The onset of sedation is 15-30 minutes with a peak effect between 30-60 minutes. The usual clinical duration is 1 hour but residual sedation may persist for longer because it has an active metabolite, trichloroethanol, which has a half life of 10 hours in toddlers, 18 hours term infants and 40 hours in preterm infants. It should therefore be considered a long acting drug and "resedation" may occur especially after stimulation has stopped.

This unpredictability dictates that, despite the safe track record, the child should be carefully monitored and only discharged when the level of sedation is clearly decreasing. Tragically airway obstruction and death has occurred in a child strapped in a car seat in the back of a car while going home following procedural sedation.

The dose should be decreased in neonates, high risk or debilitated patients especially those with significant renal and hepatic disease. It may cause arrhythmias in children with cardiac disease especially with excessive or repeat doses. Chloral hydrate is contraindicated in porphyria and in children who have previously exhibited an idiosyncratic response or hypersensitivity to its use.

Dose: 25-100mg/kg (oral or rectally) up to 1g/dose (maximum of 2g in two divided doses)

7.1.5 Droperidol - a substituted butyrophenone - has good sedative and anti-emetic properties but is only weakly anxiolytic. It is therefore usually used in combination with other sedatives.

Droperidol can be given orally (50-200ug/kg) with an onset of action of one hour, intramuscularly or intravenously (0.1-0.15mg/kg). Dysphoria, a "locked-in-feeling"(outer calm, inner turmoil) and extrapyramidal reactions are major disadvantage seen particularly when the drug is used alone.

Droperidol is currently under threat of being withdrawn from the South African market because of reports of cardiac dysrhythmias following its intravenous use.

7.2 Systemic (intravenous) anaesthetics

Intravenous anaesthetic agents can be used to provide sedation of short duration. Traditionally regarded as the domain of the anaesthesiologist, these agents are being used increasingly outside the operating theatre. This has created some difference of opinion between specialists and non-specialists.

The advantage of their short duration should not be lost by an
inadequately trained physician who, through improper use or attention to detail, allows a poorly monitored child to rapidly progress from sedation to anaesthesia with potentially fatal results. These agents are difficult to titrate and control to achieve ‘conscious sedation’ in children, particularly young children.

7.2.1 Ketamine – a phencyclidine derivative – has been widely used for the past two decades. It produces a trance-like state, with minimal cardio-respiratory depression in most children. Although it is generally believed that it causes little respiratory depression and that airway reflexes are preserved, this is not entirely true. Ketamine will maintain upper airway tone but will not protect against aspiration. Particular care should be taken with pre-mature infants, when co-administered with other CNS depressants or in children with a “full stomach”.

Ketamine stimulates both salivary and tracheobronchial secretions. The pre-emptive use of an antisialogogue, atropine or glycopyrrolate, is recommended because the copious secretions alone can cause laryngospasm.

Ketamine is sometimes associated with nonpurposeful movement which limits its use when immobility is necessary (CT scans). These movements can be reduced by small doses of midazolam. Midazolam may also be used to reduce dysphoric reactions and hallucinations during emergence but this may prolong and deepen the sedation.

Ketamine will increase the intracranial pressure (ICP) by markedly increasing the cerebral blood flow. It should be used with caution in the presence of head injury and raised ICP. It has a similar effect on the eye and raises intraocular pressure. Additional contraindications include hypertension and psychosis although it is recommended in some behavioural disorders in children (e.g. autism) in combination with midazolam.

Ketamine has been used successfully in combination with both propofol and midazolam by continuous infusion (beware of apnoea).

7.2.2 Propofol - a short acting sedative hypnotic – that is formulated in an intralipid preparation. It has no analgesic properties and therefore must be combined with some form of analgesia when used for painful procedures. Propofol has antiemetic and antipruritic properties. Intravenous injection is painful (burns) but this can be minimized by injecting into a large vein or mixing with a small dose of lignocaine. Myoclonic movements may also be seen.

Deep sedation and airway obstruction occur rapidly in children and therefore propofol should only be titrated to effect by skilled individuals who are competent in airway management. “Target controlled infusion” by computer programmed systems have improved and may provide a means to titrate sedation to a desired effect by controlling for at least some inter-individual variability. Unfortunately most existing pharmacokinetic models are inappropriate for use in children. Rapid administration may be associated with hypotension, respiratory depression and apnoea particularly in com-

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| Table II: Ketamine synopsis |
|-----------------------------|
| **Administration for analgesia - sedation** |
| Oral | Intravenous | Intramuscular | Rectal |
| Oral | Intravenous | Intramuscular | Rectal |
| Oral and rectal |
| **Onset/Time to peak effect** |
| Oral | Intramuscular | Intravenous | Rectal |
| Oral | Intravenous | Intramuscular | Rectal |
| Oral and rectal |
| **Duration of action** |
| Intravenous | Intramuscular | Oral and rectal |
| **Adverse reactions** |
| Respiratory depression - rare |
| Laryngospasm, coughing |
| Salivation, secretions |
| Hypertension, tachycardia |
| Emergence phenomena: Hallucinations |
| Paradoxical hypotension |
| Rigidity or hypotonicity |
| Ataxia |
| Random movements |
| Elevates intracranial pressure and cerebral metabolic rate |
| Nystagmus |
| Vomiting |
| May lose protective reflexes - risk of aspiration (full stomach) |
| **Drug interactions** |
| Benzodiazepines, opiates |
| Drugs metabolised by liver |
| **Special concerns** |
| Use with caution in children with full stomach / with URI |
| Anti-sialogogue recommended |
| **Antagonist** |
| None |
| **Antagonist** |
| **Adverse reactions** |
| Respiratory depression - rare |
| Laryngospasm, coughing |
| Salivation, secretions |
| Hypertension, tachycardia |
| Emergence phenomena: Hallucinations |
| Paradoxical hypotension |
| Rigidity or hypotonicity |
| Ataxia |
| Random movements |
| Elevates intracranial pressure and cerebral metabolic rate |
| Nystagmus |
| Vomiting |
| May lose protective reflexes - risk of aspiration (full stomach) |

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combination with other CNS depressants.

Fresh ampoules of propofol should always be used in view of the risk of bacterial contamination in lipid emulsions that are "preservative free". Strict sterile precautions must be adhered to when preparing infusions. With long term sedation (days) in the ICU setting fatal metabolic acidosis, myocardial failure and lipaemia have been described in children with viral respiratory disease. However this is controversial and is not universally accepted as the cause.

7.3 Opiate analgesics - antagonist naloxone

Opiate analgesics should only be used when painful procedures are to be performed. Any attempt to sedate a child with opiate analgesics is inappropriate and fraught with the danger of respiratory depression.

7.3.1:Fentanyl - a synthetic opiate - is being used increasingly to provide analgesia for short procedures in children. The onset is almost immediate when given intravenously. The usual initial dose is 0.25 - 0.5ug/kg and should given slowly and in small increments to avoid complications such as chest wall rigidity and respiratory depression.

The risk of respiratory depression is high following rapid administration and is compounded when used in combination with other CNS depressants. Close observation after the procedure is essential because the respiratory depression outlasts the analgesia. The incidence of nausea and vomiting is similar to other opiates. Other adverse effects are listed in the table below.

The fentanyl lollipop (oralet) - a sweetened raspberry flavoured lollipop - is not yet available in South Africa. The 'fentanyl patch' - a short acting synthetic opiate - has similar effects as fentanyl but is of shorter duration and less potent. Unless the procedure is expected to take only a few minutes the initial dose of 10ug/kg should be followed by an infusion with a starting rate of 1ug/kg/min. Extraboluses or changes in the infusion rate are governed by the cardiovascular response to surgery.

Neonates and infants have significantly reduced clearance and prolonged elimination. The duration of action in this age group is therefore longer.

Significant bradycardia and hypotension are frequently seen in infants and neonates and can be reduced by the pre-emptive atropine or by slow administration of a dilute solution. Other adverse effects include nausea and vomiting, chest wall rigidity and respiratory depression (particularly in combination with other CNS depressants).

7.3.3: Remifentanil - the newest ultrashort acting synthetic opiate - is an extremely potent, rapid onset narcotic of short duration. Its action is terminated by nonspecific tissue and plasma esterases. In view of its short duration it should be given by continuous infusion (0.05ug.kg.min), Bradycardia, hypotension, rapid onset of respiratory depression and chest wall rigidity precludes its use by untrained physicians.

Remifentanil's use in children, particularly outside the operating theatre setting, is limited.

7.3.4: Morphine - a long acting opiate - should only be considered for painful procedures of long duration or when analgesia is required post procedure e.g. burn dressing, reduction fracture.

Morphine may be given orally (0.2-0.5mg/kg), intramuscularly (dose 0.1-0.2mg/kg), or intravenously (0.05-0.1mg/kg; maximum 0.3mg/kg). The time to peak effect is approximately 60 minutes following oral administration, 10-30 minutes intramuscularly, and 3-5 minutes intravenously. The duration of action after IV administration is 3-4 hours.

Adverse effects include respiratory depression, particularly in association with other CNS depressants, hypotension (partly due
to histamine release), dysphoria, delirium, nausea, vomiting, smooth muscle spasm (biliary, ureteric), urinary retention and pruritus.

Special precautions should be taken with critical ill patients who are not ventilated, neonates and children with upper airway obstruction or asthma.

7.3.5: Pethidine – a long acting synthetic opiate – is very popular in South Africa but should only be used for longer procedures or when analgesia is required post procedure.

Pethidine may be given orally (1-2mg/kg), intramuscularly (1-2mg/kg) or intravenously (0.5-1mg/kg). The onset time is slow when given orally or intramuscularly. The time to peak effect is 30-90 minutes. Intravenously, the onset time is 1-3 minutes.

The duration of action is 2-4 hours. The duration of action in neonates is variable and prolonged, the elimination half life may vary from 3-59 hours. It therefore not recommended for use in neonates. Long term use should also be avoided because the active metabolite (nor-meperidine) may cause convulsions. Naloxone reversal after chronic use may precipitate seizures caused by nor-pethidine.

Central nervous system toxicity may occur in children taking phenothiazines or tricyclic antidepressants. Phenytoin may reduce the analgesic effect of pethidine.

Adverse effects include respiratory depression, delirium, nausea and vomiting, urinary retention, pruritis and hypotension (histamine induced).

7.3.6: Tildine – a potent semi-synthetic opiate – is administered sublingually in droplet form from a specific dispenser. One ml contains 100mg in 15% alcohol. Each droplet contains 2.5mg. The current recommended dose is 1mg/kg whereas previously 1 drop per year of age was recommended. This was totally inadequate for analgesia in younger children.

Adverse reactions are similar to other opiates and include respiratory depression particularly in neonates, ex-premature infants and children with chronic lung disease and cardiac dysfunction.

7.3.7: Naloxone – is a specific opiate antagonist which will reverse opiate induced analgesia and respiratory depression in parallel. Naloxone should be readily available whenever opiates are used. It should not be used routinely for reversal of the sedative effects of opiates but reserved for respiratory arrest or severe respiratory depression.

Naloxone may be given subcutaneously, intramuscularly or intravenously but intravenous is the preferred route in an emergency. The initial dose of 1-2ug/kg should be titrated to effect every 2-3 minutes. 10-100ug/kg may be required for a respiratory arrest. Rapid injection will not only reverse the respiratory depression and sedation but also the analgesia which may result in significant sympathetic and cardiovascular stimulation (in particular hypertension).

The duration of action is short and respiratory depression may recur. It is therefore essential to observe the child for a minimum of 2 hours after its use. Similar doses may be repeated as necessary.

Adverse effects following reversal include nausea, vomiting, tachycardia, hypertension, delirium and pulmonary oedema.

7.4. Inhalational agents

7.4.1: Nitrous oxide – is an anaesthetic gas with analgesic properties used in combination with oxygen. It is easy to use and noninvasive. Nitrous oxide has a peak effect of 3-10 minutes and is characterised by a rapid return, within minutes, to baseline when discontinued.

Entonox is a mixture of 50% nitrous oxide and 50% oxygen. In concentrations used for procedural sedation it is a weak analgesic, sedative and anxiolytic but it may rapidly produce deep sedation or anaesthesia when used in combination with sedatives, hypnotics or systemic analgesics.

Nitrous oxide should only be used for ASA 1 and 2 patients since it may cause myocardial depression in patients with compromised cardiac dysfunction. It may alter the ventilatory response to hypoxia in children with respiratory disease. Supplementary oxygen should always be given at the end of the procedure to prevent ‘diffusion hypoxia’. Nitrous oxide also increases cerebral blood flow and should be used with caution in the presence of head injury and raised intracranial pressure. Side effects include headaches, nausea and vomiting.

Contraindications to its use include pneumothorax, respiratory failure, depressed level of consciousness, otitis media, bowel obstruction, or any other situation where diffusion into an air filled space could compromise the child’s safety or comfort.

Adequate scavenging should be available to prevent pollution of the environment and to protect personnel.

7.5: Local anaesthetic agents

Analgesia provided by local infiltration or specific nerve blocks are extremely useful adjuncts for painful procedures to be performed under sedation and analgesia. It is beyond the scope of these guidelines to outline specific nerve blocks and the readers are referred to standard texts on paediatric regional anaesthesia.

The toxicity of local anaesthesia is always a concern and should never be used without appropriate resuscitation equipment available. Local anaesthetics are commonly used in combination to speed the onset of action but this practice is unnecessary in children because generally the onset is more rapid than in adults. When used in combination the toxicity of local anaesthetics are additive.

Adrenaline (1:200000) produces vasoconstriction and thereby prolongs the duration of action and reduces systemic absorption. The younger the child the greater the prolongation of action. Adrenaline can cause tissue ischaemia and should not be used in proximity to end-arteries (digits, ear, penis).

The recommended maximum safe dose for commonly used agents are as follows: lignocaine 5mg/kg (with adrenaline 7mg/kg); bupivacaine 2-3mg/kg (with adrenaline 3-4mg/kg); and ropivacaine 3mg/kg (not available with adrenaline).

7.5.1: EMLA cream (eutectic mixture of local anaesthetics) consists of lignocaine 2.5% and prilocaine 2.5%). It provides topical analgesia to skin and mucous membranes. When the cream is applied to the skin for 60 minutes prior to the procedure it can reduce the pain of IV placement, lumbar puncture and removal of superficial skin lesions (circumcision, warts, molluscum contagiosum, small skin grafts).

The slow onset is a major disadvantage. Other rare adverse effects include skin blanching, erythema, itching, rash and methaemoglobinemia. The methaemoglobinemia is related to absorption of large amounts of prilocaine in susceptible individuals or through large open wounds. It is therefore contraindicated in burns, in neonates particularly premature infants, patients with congenital methaemoglobinemia or infants receiving other methaemoglobin-inducing drugs (phenytoin, sulpha drugs, phe- nobarbitone, acetaminophen)
7.5.2: Ametop (amethocaine gel) has a similar effect with a more rapid onset (30-40min) and better vasodilatation. A higher incidence of allergic reactions has been reported. It’s availability in South Africa is limited.

7.6: Lytic cocktails
So called ‘lytic cocktails’ i.e. combinations of opiates (pethidine, methadone), phenothiazines (phenergan, trimeprazine) and butyrophenones (droperidol) have been used extensively in the past and remain popular despite the risk. These agents are all long acting and in combination carry significant risk of prolonged life-threatening respiratory depression and sedation (7-15hours), extrapyramidal symptoms, seizures and hypotension. The use of these ‘cocktails’ should be abandoned for outpatient procedures.

7.7: Alpha -2-agonists
These agents are gaining in popularity, used alone or in combination with other sedatives or opiates. Oral clonidine is currently available in South Africa. However, dexmetomidine is only available for study purposes.

8. Conclusion
No child should suffer unnecessary pain or distress. These guidelines have been drawn up to assist all those devoted to the care of children to achieve this goal with maximum safety and efficiency during therapeutic or diagnostic procedures. There is increasing evidence that for procedural sedation, organisational and educational issues are more critical than pharmacological ones regarding safety.

There needs to be a creative and non-territorial approach to this issue. The cost of monitoring equipment is negligible when compared to the cost of an MRI. MRI compatible monitors are absolutely essential for the safety of the child in the MRI suite but few are available.

Health care managers and providers need to develop a system to provide an appropriate and effective safety net. Hospital administrators, nursing administrators and physicians involved must together develop appropriate methods of sedation, training and education for the safe provision of therapeutic and procedural sedation in children.

Regular reviews of hospital policies and procedures will identify areas with inadequate equipment, inadequate monitoring or inadequate screening. These must then be corrected in a cost-effective manner. The safety of children should not be compromised by frugal economic policies or for financial gain.

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