Great Ormond Street Hospital for Children NHS Trust

10: Analgesia, Sedation and Neuromuscular Blockade on PICU

Author: Andy Petros 2004
Updated: Sophie Skellett, November 2006
Updated: Shruti Agrawal, March 2011

Associated clinical guidelines/protocols:

- Use of Train of Four in assessment of the muscle relaxed patient
- Scoring for neonatal abstinence NICU

Fundamental Knowledge:
List of topics relevant to PIC that will have been covered in membership examinations.
They will not be repeated here.
Physiology:

- Afferent nociceptive pathways, dorsal horn, peripheral and central mechanisms, neuromodulatory systems, supraspinal mechanisms,
- Visceral pain, neuropathic pain

Information for Year 1 ITU Training (basic):

Year 1 ITU curriculum

Pain management:

- Assessment of pain and general principles
- **Simple analgesics:** paracetamol, NSAIDs:indications, side effects and complications.
- **Narcotics:** mechanisms of action, tolerance, toxicity,
- **Clonidine**
- NCA & PCAs
- Regional anaesthesia: Epidurals: drugs used, assessment of sensory level

Sedation:

- **General principles:** including monitoring depth of sedation. BIS monitoring covered in "monitoring in ITU" module.
- **Antihistamines**
- **Benzodiazepines:** indications, complications, reversal agents
- **Thiopentone** for barbiturate coma – continuous EEG monitoring covered in "CNS anatomy & physiology" module.
- **Ketamine:** association with hallucinations, maintenance of airway reflexes, can increase ICP.

Muscle Relaxants:

- **Depolarising muscle relaxants:** side effects and contra-indications
- **Non depolarizing muscle relaxants** mention short-acting agents.

Curriculum Notes for Year 1:

Pain Management

Assessment of pain and general principles

There is an increased awareness regarding the assessment and management of pain in children and this has been highlighted by the Royal College of Paediatrics and Child Health. Studies have demonstrated that children receive analgesia far less frequently than adults when presenting with painful conditions and younger children receive analgesia less frequently than older children. This is probably due to the fact that the younger the child, harder the assessment of pain. A number of pain assessment tools and scales have been developed for children, though most studies have concentrated on postoperative pain in children. A description of all the systems developed is outside the scope of this module but appendix 1 describes the pain assessment tool used on the neonatal unit at GOSH, which has recently been studied. Other scoring systems used in the emergency room or on paediatric intensive care include the TPPPS and TPPS (toddler preschooler postoperative pain system and toddler preschooler pain system)[1], the Beyer-Oucher[2] and behavioural scoring system developed by Hannallah[3]. Whatever the system used it is important that the system should be simple to employ and reproducible between different users to be a useful tool.

If a child is preverbal, intubated or otherwise unable to speak then their behaviour, facial expression, position and movement should be evaluated to determine the presence and severity of pain. Any assessment used should be repeated to determine the patient's response to analgesics. Successful analgesia includes reduction in irritability, longer periods of sleep, longer attention span, good eye contact and willingness to participate in play.

Physiological and behavioural variables commonly measured are:

- Blood pressure
- Heart rate changes
- Facial expression
- Body movements
- Presence of tears
- Intensity and quality of crying
- Levels of adrenal stress hormones

On the neonatal intensive care the management of pain has become an important issue. It had been thought previously that newborns did not feel pain because their nervous systems are too immature; there was also a general reluctance to use analgesic and anaesthetic drugs because of concerns about their safety in this population. Research would suggest however that this is an untenable position. Peripheral receptors, nerve pathways, and the cerebral cortex function to process pain by mid-gestation (Anand, 1993) Newborns appear to be as sensitive to pain as adults, AND preterm infants are more sensitive to pain. Neurotransmitters in the dorsal horn of the spinal cord are associated with nociception and increased somatosensory excitability in the preterm spinal cord. On the other hand, neurotransmitters in descending inhibitory nerve fibers are only present at term. Thus, there is diminished inhibition of pain in premature infants. Research suggests that there are not only short term effects of pain in neonates, there are long term effects due to permanent structural and functional changes (Porter et al, 1999) which alter the pain sensitivity in preterm infants. The hypothalamo-pituitary responses to stress are modified by sensory experiences during the neonatal period, due to plasticity of the neonatal limbic structures and expression of corticosteroids and vasopressin receptor systems regulating HPA (Francis et al, 1996)

There are a number of non-pharmacological methods of pain reduction available that staff should consider in appropriate circumstances. These include:

- Watching television (if awake enough): A study in Archives of Disease in Childhood by Bellieni et al showed that watching TV was more effective than even active distraction by the child's mother when venepuncture was being performed. The authors concluded this was due the emotional participation of mothers in the active procedure[4].
- Parents. Parents are the most powerful method of non-pharmacological pain relief available to the child. They instinctively provide comfort and therapeutic touch. Children may appear more distressed as they feel more comfortable expressing discomfort to their parents.

- Play. Play can be used not only to distract but as a method to explain medical procedures reducing associated anxiety and hence pain.
- Touch
- Music and distraction

Simple Analgesics

Anti-inflammatory drugs

Prostaglandins do not produce pain, they sensitise peripheral nerve endings to agents such as histamine and bradykinins. Most non-steroidal anti-inflammatory drugs (NSAIDs) work by inhibiting cyclo-oxygenases which produce prostaglandins.
When stable non-steroidals per rectum may be very useful. Care should be taken in renal compromise, clotting and platelet disorders. There have been some recent reports about poor bone healing with these drugs.

Drug	Dose	Interval
Diclofenac	1 mg/kg	8-12 hrly
Ibuprofen	2.5 -10 mg/kg	6-8 hrly
Ketorolac	0.2 mg/kg	4-6 hrly

Ibuprofen

This is a propionic acid derivative licensed for use in infants over 6 months for relief of mild to moderate pain, inflammation associated with soft tissue injuries and for relief of fever. If taken orally peak action is at 30 minutes; the half life is 6 hours. Ibuprofen is highly protein bound; it is hepatically metabolised and renally excreted.
Caution: Use cautiously in children with history of asthma and other allergic disorders; caution also in renal, cardiac and hepatic impairment as all NSAIDS reduce renal blood flow and hence GFR.
Side effects: GI discomfort, nausea, diarrhoea, occasional bleeding and ulceration though this will be usually with chronic regular treatment (Children appear to tolerate NSAIDs better than adults). Rashes, bronchospasm, tinnitus, fluid retention, renal failure.

Paracetamol

This is not an anti-inflammatory but has centrally acting analgesic and antipyretic properties. It is metabolised in the liver and renally excreted. Rectal pararcetamol can be useful in providing analgesia. Higher doses are required when used rectally, 40mg/kg stat then 30mg/kg 6hrly. Oral dose is 20 mg/kg qds.
Intravenous paracetamol is has been used in children quite successfully. There is also considerable data on its pharmacokinetics in neonates and there are case reports of its use in term neonates. A loading dose of 15mg/kg intravenous paracetamol over 15 minutes followed by regular infusion of 10 mg/kg every 4 hours can be used.
Pharmacokinetics: The half life of paracetamol is 2 hours; it is not protein bound; peak effect is at 30 -60 minutes; 3% urinary excretion with mostly hepatic microsomal metabolism.
Side effects: Well tolerated in usual therapeutic doses, occasional rashes or haematological disturbances (thrombocytopenia, neutropenia, leucopenia) with prolonged use. Hepatic necrosis after overdose 150 – 250 mg/kg; 90% patients will have severe hepatic damage if level 4 hours after ingestion is > 300 mcg/ml.

Narcotics

Opioids

Useful for the treatment of pain mediated by C fibres, dull, visceral pain. Opioids are all drugs, synthetic or naturally occurring which bind to opioid receptors. The μ and κ opioid receptors are associated with analgesia. However centrally mediated respiratory depression are also μ and κ associated. Morphine is a μ agonist.

Morphine

Morphine is one of the most frequently used opioids in PICU to provide sedation and analgesia. It also provide anxiolysis and sedation. It is frequently the only agent used in neonates but is combined with midazolam infusions in infants and children. Its elimination half-life is about 9

hours in the preterm, about 7 hours in the neonate but only about 5 hours in the older infant. Morphine is metabolised in the liver and metabolites are excreted in the urine. The active metabolite morphine-6-glucuronide further prolongs its activity.
Morphine is useful for severe pain and confers a state of euphoria and mental detachment.
When small doses are used 0.1 mg/kg (iv, im) are given analgesia usually occurs without loss of consciousness. Oral morphine has low bioavailablity therefore large doses of morphine have to be used if given orally x3 – x5 the intravenous dose is required.
Side Effects: Commonly causes nausea and vomiting, constipation and drowsiness. Large doses cause respiratory depression and hypotension. Neonates, particularly if preterm, may be more susceptible. It may cause muscle rigidity in some patients. Morphine should not be used in children with an asthma attack as it can cause histamine release with worsening bronchospasm; for the same reason avoid use in phaeochromocytoma as histamine release can have a further pressor effect.
Cautions: Effect prolonged in hepatic and renal failure.
Morphine's safety profile includes long term follow-up studies that have demonstrated no adverse CNS developmental effects from its use in infants and neonates.

Fentanyl
Fentanyl is 100 times more potent than morphine and is cardiovascularly stable over a wide range of doses. There is a large variability in requirements to achieve similar levels of sedation. It has a rapid onset of action (1-2 minutes) and brief duration of action and prevents the biochemical and endocrine stress response to painful stimuli that may be detrimental in seriously ill patients. Hence is favoured for procedures such as:

- Bone marrow aspiration
- Fracture reductions
- Dental procedures
- Dressing changes

Rapid infusions of fentanyl can be associated with chest wall rigidity which can make ventilation difficult; muscle relaxants will improve this. Fentanyl and Alfentanyl not only have fewer cardiovascular side effects but also produce less histamine release.
The dose for procedures is 2 -5 mcg/kg intravenously if used in the setting of other background analgesia. The dose for infusion:
Neonate 1.5 mcg/kg/hour
Child 1 – 6 mcg/kg/hour
Cautions: In severe renal failure or hepatic failure.

Remifentanil
This is a very short acting potent opioid ideal for stimulating procedures such as physiotherapy or chest drain removal. Also useful as a short acting sedative agent and may replace propofol in PICU. Ideal for neurosedation as it can be stopped and allow the child to awake to get a window of awareness consciousness. Remifentanil is not metabolised in the liver like the other opioids, instead it undergoes rapid metabolism by non-specific blood and tissue esterases. There is little evidence to support the use of remifentanil in neonates.
Dose: Child (1-12 yrs) 1 mcg/kg intravenously then an intravenous infusion of 0.05 – 1.3 mcg/kg/minute.
Child (12 –18 yrs) 0.5 – 1 mcg/kg iv, then 0.05 – 2 mcg/kg/minute infusion.

Methadone
Potency about the same as morphine but has a much longer duration of action, half-life 12-24hrs. Dose 0.1-0.2mg/kg 6-12hrly orally. It is less sedating than morphine. Methadone is used to wean from morphine/ heroin dependency and for intractable pain. Useful as it has high oral bioavailability. If the mother is on methadone this will be present in breast milk so can affect the decision on whether or not to breast feed – the baby must be monitored for respiratory depression. Methadone can be used in neonatal abstinence syndrome.

Opioid Dependence and Withdrawal
Psychological dependence rarely occurs in children when opioids are used for pain relief but tolerance can develop during long term treatment; they should be withdrawn gradually to avoid abstinence symptoms. The mechanism by which opioids cause tolerance and physiological

dependence have not been firmly established. Several mechanisms have been proposed involving changes in opioid receptor number, structure or binding affinity.
If narcotic therapy has been continuously given for 4 to 5 days or longer or if high doses have been administered gradual withdrawal should be considered. The probability of withdrawal approaches 100% after infusions lasting > 9 days.
Gradual weaning involves a decrease in the dose by approximately 5 – 10 % per day. A protocol exists on PICU and NICU for the gradual withdrawal of morphine. Clonidine can be useful as a morphine sparing drug and help in control of withdrawal symptoms[6].
Symptoms of acute withdrawal: agitation, sweating, nausea, vomiting, hypertension, salivation, extreme discomfort (this is **not** psychological drug addiction).

Opioid Toxicity
Overdose of opioids will cause respiratory depression and apnoea, hypotension and CNS depression. These effects can be reversed immediately by intravenous Naloxone which is an opioid antagonist, antagonising the mu and kappa receptors. Naloxone is a competitive inhibitor so the dose may have to be tailored to the dose of opioid given rather than the child's weight. The dose may have to be repeated or an infusion started in some cases as the half life of Naloxone is short. This should be used carefully in children requiring on going analgesia because the analgesic effect of opioids is also antagonised. Naloxone can also be used to reverse the respiratory depression in neonates whose mothers have received opioid analgesia prior to birth.
Dose: Neonate 10 mcg/kg iv
Child (1 month – 12 yrs) 10 mcg/kg iv dose or 5 – 20 mcg/kg/hour iv infusion.

Table 7 .Potency and half-life of commonly used opioids

Drug	Potency	Half-life (hrs)
Morphine	1	2-3
Pethidine	0.1	2-3
Methadone	1	12-24
Alfentanil	20	0.2-0.3
Fentanyl	100	0.3-0.5
Remifentanil	100	0.1
Sufentanil	1000	0.2-0.4

Clonidine
A centrally acting alpha-2 agonist has sedative and anxiolytic properties. It also has a significant role in reducing symptoms of withdrawal. Clonidine is believed to block the symptoms of withdrawal by decreasing the amount of norepinephrine released into the synaptic cleft and reducing the firing rate of noradrenergic neurons within the Locus Coeruleus. The locus coeruleus is an area with a high density of opiate receptors Neuronal hyperactivity in this area may be associated with the development of withdrawal.

Clonidine has good analgesic effect with much less sedation than opioids. Clonidine hence has a role on PICU in:

- Opioid withdrawal
- Pain relief
- Morphine sparing effect/ benzodiazepine sparing [7]

Dose: A test dose of 1 mcg/kg PO is given to assess the hypotensive response; if well tolerated a further 2 mcg/kg can be given 20 – 30 minutes later and the patient started on 3 mcg/kg PO tds.
Clonidine can also be given as an infusion 0.1 – 2mcg/kg/hr.
Pharmacokinetics: half life is 9 hours, 50% metabolised in the liver, 50% excreted in the urine
Side Effects: Dry mouth, sedation (though much less than opioids), bradycardia, hypotension, headache, Raynaud's phenomenon, sudden withdrawal can cause a hypertensive crisis.

NCAs and PCAs

Although they are popular, simple continuous infusions of analgesia are very limited by the fact that for pharmacokinetic reasons changes in infusion rate will only change the level of analgesia very slowly. In addition, this "lag effect" can lead to analgesic drug accumulation and escalation of the total dose of analgesia to unnecessarily high levels. Because there is so much variation in the

amount of analgesia individual patients need, getting the right dose with a continuous infusion is very difficult.

PCA is patient controlled analgesia. Superior pain relief has been achieved through the use of PCA. This method of delivery uses computerized infusion pumps that deliver a specific amount of the analgesic (usually morphine) continuously. Bolus administration of the drug on top of this background is also available when the PCA is activated by the patient to treat break through pain. Lockout periods and dose limits can be programmed. PCA is effective in the management of pain in children $\geq$ 7years, but younger ages will find this more difficult (they will find it difficult to understand and may lack the manual dexterity or strength to operate the pump); for this group NCA (nurse controlled analgesia) is more appropriate.

NCA uses PCA technology i.e. specially designed microcomputer controlled infusion pumps to allow safe delivery of analgesia. The pumps will only allow a pre-determined amount of analgesia to be given within safe limits. However, the effectiveness of NCA, and its safety, depend on a number of factors:

- NCA Patient selection and education
- Correct NCA equipment set-up
- Appropriate supervision and monitoring of NCA

Monitto and Greenburg 2000 studied the use of NCA in children[5]. They concluded that NCA appears to provide superior analgesia to that reported when prn dosing of analgesics in young children is assessed by objective measures. Although NCA was safe in the large majority of patients studied, some patients did experience opioid-induced side effects, most notably respiratory compromise. They reported a 1.7% incidence of apnea and episodes of desaturation requiring treatment with naloxone. They did however allow parents and or nurses to determine pain levels and dosing and did not study the effect of this use of different groups on doses given.

At Great Ormond Street Hospital there is a Pain Control Team available for advice and for initiating PCA and NCA. The assessment for infusion doses is based on the patient's requirements and careful pain assessments. The details of this service and further information regarding NCAs and PCAs can be found on their website on the GOSH intranet.

Regional Anaesthesia

These enable effective analgesia with fewer systemic side effects such as respiratory depression and they are morphine sparing. These analgesics may require placement of catheters to enable injection of local anaesthetics and narcotics into the pleural or epidural space or to block peripheral nerves.

Action:

Local anaesthetics cause reversible interruption of the conduction of impulses in peripheral nerves. The primary electrophysiological effect of these compounds is to cause a local decrease in the rate and degree of depolarisation of the nerve membrane such that the threshold potential for transmission is not reached and the electrical impulse is not propagated down the nerve. There is no effect on the resting or threshold potential, although the refractory period and repolarisation may be prolonged. These effects are due to blockade of sodium channels, thereby impairing sodium ion flux, across the membrane.

The drugs used vary widely in their potency, toxicity, duration of action, stability, solubility in water and ability to penetrate mucous membranes. These variations determine their suitability for use by various routes e.g., topical (surface), infiltration, plexus, epidural or spinal block. LAs do not rely on the systemic circulation to transport them to their site of action, but uptake into the systemic circulation is important in terminating their action and producing toxicity. Following most regional anaesthetic procedures, maximum arterial plasma concentrations develop within about 10 to 25 minutes; so careful watching for toxic effects is necessary during the first 30 minutes after injection. Great care must be taken to avoid accidental intravascular injection[9].

Local anaesthetics may be applied to the skin, the eye, the ear, the nose and the mouth as well as other mucous membranes. In general, cocaine, amethocaine, lignocaine and prilocaine are the most useful and effective local anaesthetics for this purpose. When

used to produce topical anaesthesia, they usually have a rapid onset of action (5-10mins) and a moderate duration of action (30-60 mins). Cocaine is a potent vasoconstrictor and is useful in the reduction of bleeding as well as topical anaesthesia.

There are 2 classes of local anaesthetic drugs defined by the nature of the carbonyl-containing linkage group. The ester agents include cocaine, procaine, amethocaine and chloroprocaine, whilst the amides include lignocaine, prilocaine, mepivacaine and bupivacaine. There are important practical differences between these two groups of local anaesthetic agents. Esters are relatively unstable in solution and are rapidly hydrolysed in the body by plasma cholinesterase (and other esterases). One of the main breakdown products is para-amino benzoate (PABA) which is associated with allergic phenomena and hypersensitivity reactions. In contrast, amides are relatively stable in solution, are slowly metabolised by hepatic amidases and hypersensitivity reactions to amide local anaesthetics are extremely rare. In current clinical practice esters have largely been superseded by the amides.

Toxicity:

Complications of these techniques include those of catheter placement, narcotic effects and local anaesthetic toxicities.

Toxic effects associated with LAs usually result from excessively high plasma concentrations. Toxic effects initially include a feeling of inebriation and lightheadedness followed by sedation, circumoral paraesthesia and twitching: convulsions can occur in severe reactions. LAs are also cardiotoxic (in high enough systemic doses) causing severe bradyarrythmias, sinus arrest, a negative inotrope effect and depressed contractility.

When prolonged analgesia is required a long acting LA is preferred to limit toxicity. LA injections should be given slowly so that possible inadvertent intravascular injection can be rapidly detected. LA should not be injected into inflamed or infected tissues (increased absorption will occur with increased risks of toxicity)[9].

Use of vasoconstrictors:

Most LAs cause vasodilatation (except cocaine). The use of vasoconstrictors in combination limits systemic absorption and hence toxicity; it will also prolong the duration of action. Adrenaline is commonly used (concentration 5mcg/ml). Adrenaline containing solutions should **never** be used for infiltration around end-arteries i.e. penis, ring block of fingers or other areas with a terminal vascular supply as the intense vasoconstriction may lead to severe ischaemia and necrosis.

Lignocaine for surface anaesthesia:

Effectively absorbed from mucous membranes and is a useful surface anaesthetic in concentrations of 2 – 4%.

Solutions of Lignocaine 1% used otherwise; duration of action when combined with adrenaline is 90 minutes.

Surface preparations:

a. Lignocaine gel 1% for mucocutaneous anaesthesia: mouth ulcers, urethral catheterisation (combined with chlorhexidine).
b. Lignocaine ointment 5%: local relief anal fissures, haemorrhoids, herpes zoster.
c. Lignocaine solution 4%: spray for bronchoscopy.
d. Lignocaine cream: (children over 1 year). EMLA cream is a eutectic mixture of local anaesthetics which may be used to provide surface anaesthesia of the skin . It is a mixture of the base forms of lignocaine 2.5% and prilocaine in equal proportions in an emulsion. Cutaneous contact (usually under an occlusive dressing) should be maintained for at least 60 minutes prior to venepuncture.

Infiltration local anaesthesia:

Conduction anaesthesia can be divided into minor nerve blockade (e.g. ulnar, radial or intercostal), and major blockade of deeper nerves or trunks with a wide dermatomal distribution (e.g. brachial plexus blockade). For each individual agent the duration of anaesthesia will be determined more by the total dose of the drug rather than the volume or concentration of drug used.

Infiltration techniques are used to provide anaesthesia for minor surgical procedures. Amide anaesthetics with a moderate duration of action are commonly used (lignocaine, prilocaine and mepivacaine). The site of action is at unmyelinated nerve endings and onset is almost immediate. The duration of local anaesthesia is variable. Procaine has a short duration of action (15-30 min), while lignocaine, mepivacaine and prilocaine have a moderate duration of action (70-140 min). Bupivacaine has the longest duration of action (approximately 200 min). The addition of adrenaline (1 in 200,000) will increase the quality and prolong the duration of anaesthesia.

Lignocaine

Injection of Lignocaine into the skin locally to minimise the pain of chest drain insertion, stitching, lumbar puncture etc.

i. Neonates: up to 3 mg/kg (0.3 ml/kg of 1% solution) 4 hourly max.
ii. Child 1 month – 12 years: up to 4 mg/kg (0.4 ml/kg 1% solution) 4 hourly max.
iii. Child 12 – 18 years: up to 200 mg, max 4 hourly.

Bupivacaine

Bupivacaine has a long duration of action (3-7 hours). It has a slow onset of action taking up to 30 minutes for full effect. Often used in lumbar epidural blockade. It is the principal drug for spinal anaesthesia. Preparations with and without adrenaline are available.

Epidural anaesthesia:

Is commonly used during surgery, often combined with general anaesthesia, because of its protective effect against the stress response of surgery. It is often used when postoperative pain relief is essential. An epidural is a specialised procedure performed by an appropriately trained doctor, usually an anaesthetist.

The needle is inserted through the skin into the epidural space. A fine plastic catheter is threaded through it, and the needle is removed. The catheter is taped in place and LA and analgesics are infused through it. Local anaesthetic solutions are deposited in the epidural space between the dura mater and the periosteum lining the vertebral canal. The epidural space contains adipose tissue, lymphatics and blood vessels. The injected local anaesthetic solution produces analgesia by blocking conduction at the intradural spinal nerve roots.

The quality and extent of the blockade produced by each agent is determined by the volume as well as the total dose of the drug. Epidural catheters can be placed in either the cervical, thoracic or lumbar regions. Epidural infusions are usually run for 2-3 days and rarely for longer than 5 days.

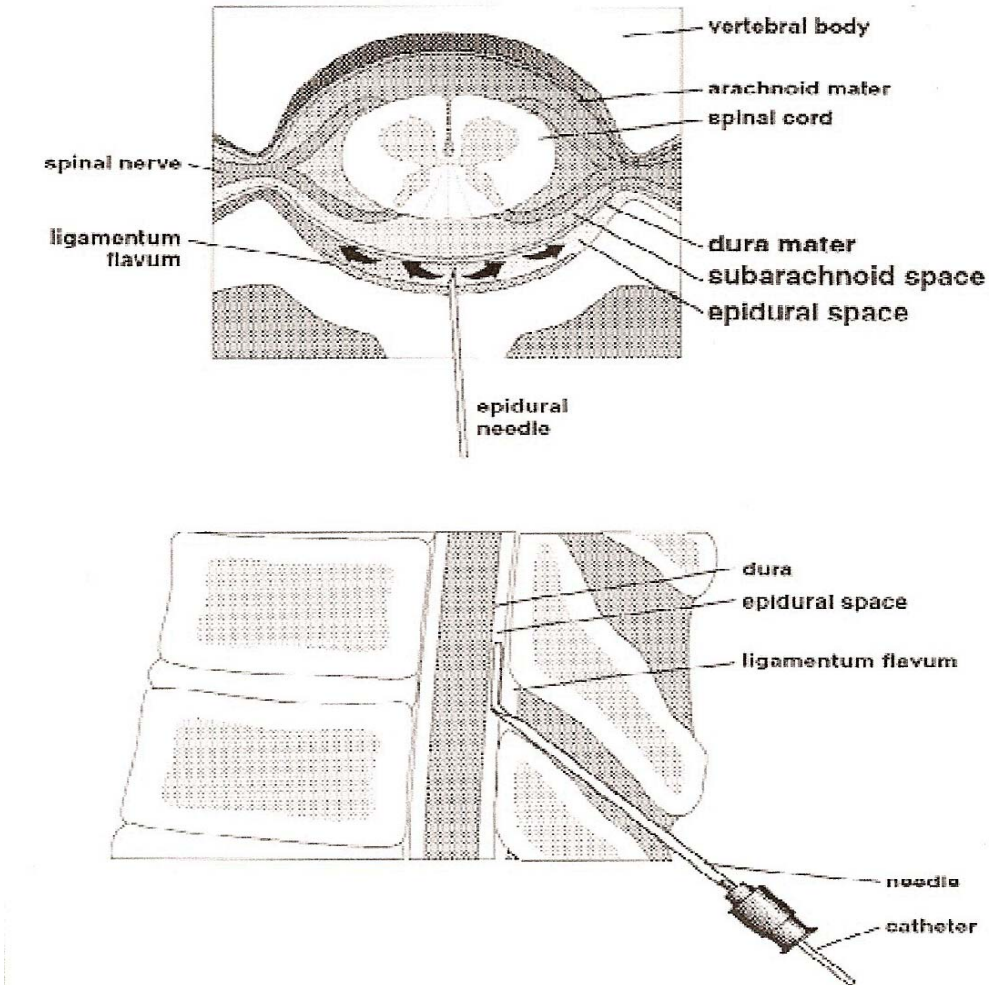
Bupivacaine (0.5%) or lignocaine (1.5-2.0%) are usually used to produce extradural anaesthesia. Repeated administration of lignocaine or mepivacaine into the epidural space may result in a diminished response with each subsequent dose (tachyphylaxis)

Spinal Anaesthesia:

The introduction of local anaesthetic solutions directly into the cerebrospinal fluid (CSF) produces spinal anaesthesia. The local anaesthetics do not have to cross tissue or diffusion barriers and also the central attachments of the ventral and dorsal nerve roots are unmyelinated, which allows rapid uptake of the free base. There is a faster onset of action and a smaller dose is required. Spinal anaesthesia produces a similar clinical effect with a dose approximately ten times smaller than that needed for extradural anaesthesia.The greatest challenge in spinal anaesthesia is to control the spread of local anaesthetic through the cerebrospinal fluid (CSF) to provide a block which is adequate for the proposed surgery without unnecessary extensive spread, and increased risk of complications.

Solutions of amethocaine (0.2%), lignocaine (5%), prilocaine (5%) bupivacaine (0.5%) and mepivacaine (4%) are commonly used to produce spinal anaesthesia. Prilocaine and mepivacaine have a slightly longer duration of action than lignocaine; bupivacaine has the longest duration of action.

The following analgesics may be separately added to the local anaesthetic solution to improve analgesia: Fentanyl, Morphine, Clonidine.



UWHC Authority Board 2000, Wisconsin.

Assessment of sensory level

It is important to assess sensory block:

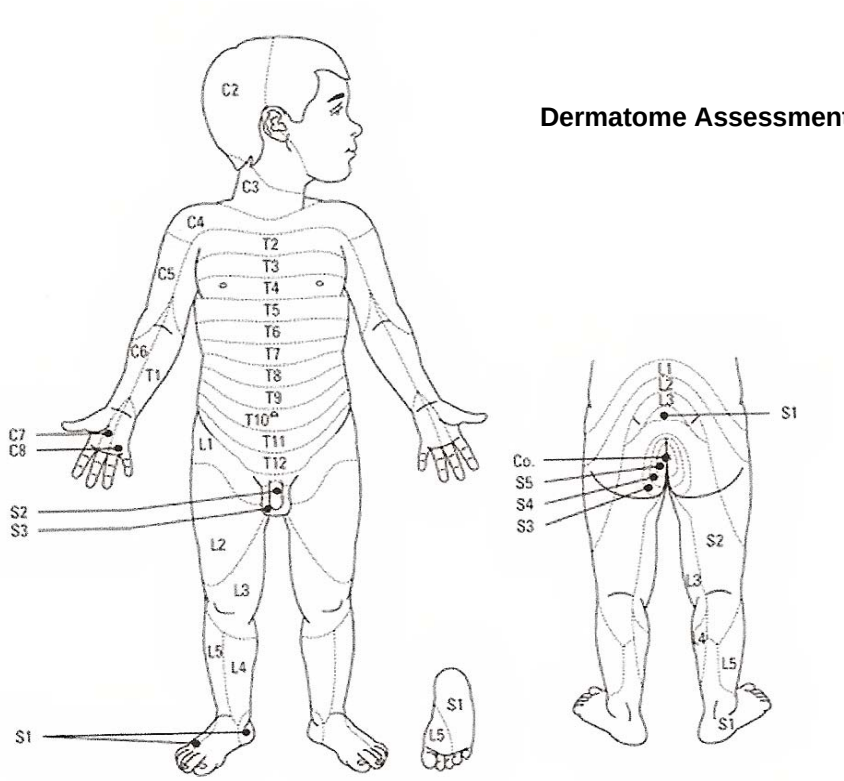
To ensure the spinal/epidural/caudal is covering the patient's pain.

To ensure the block is not too extensive, which may increase the risk of complications.

Assessment should be performed on both sides of the body as blocks may be uneven or unilateral. Ice or ethyl chloride spray, which produces a cold sensation, can be used to assess the level. Once ascertained the level of the block must be documented. Record both the upper and lower limits of the block:

eg T7-L1 L = R or R: T7-L1 L: T10-L2

Regular assessments should take place and in addition if the rate of epidural/spinal is increased or the patient complains of pain then the level should be reassessed. Epidurals and spinals are placed and monitored by the pain team who should be contacted if there are any problems or if the level of the block is higher than expected.



Dermatome Assessment

www.rch.org.au

Sedation

- **General principles**
- **Antihistamines**
- **Benzodiazepines**
- **Thiopentone** for barbiturate coma – continuous EEG monitoring covered in "CNS anatomy & physiology" module.
- **Ketamine**

Sedation is an essential component of the management of intensive care patients. It is required to relieve the discomfort and anxiety caused by procedures such as tracheal intubation, ventilation, suction and physiotherapy. It can also minimize agitation yet maximize rest and appropriate sleep.
Oral sedation is a frequently employed route in paediatrics and agents such as Chloral and Vallergan are used. Intravenous sedation involves the use of incremental doses of primarily benzodiazapines agent to reduce the child's level of consciousness to allow relatively minor yet stimulating procedures to be performed.
It must be remembered that sedative are not analgesics and this can result in restlessness and agitation when children are unable to localise the pain or discomfort they are experiencing. Hence the judicious combination of sedative and analgesia can produce ideal conditions for minor procedures. Simple sedation results in calm co-operative children.

Table 1 Drugs commonly used for sedation in children

Benzodiazapines
Phenothiazines
Buterophenones
Anti-histamines
Chloral Hydrate
Ketamine
Barbiturates
Opioids

Adequate sedation and analgesia ameliorates the metabolic response to surgery and trauma. Too much or too little sedation and analgesia can cause increased morbidity e.g. oversedation can cause hypotension, prolonged recovery time, delayed weaning, gut ileus, DVT, nausea and immunosuppression; undersedation can cause hypertension, tachycardia, increased oxygen consumption, myocardial ischaemia, atelectasis, tracheal tube intolerance and infection.

Monitoring:

The combined use of sedation and analgesia for noxious procedures is potentially hazardous as it may result in the loss of protective laryngeal airway reflexes and should only be employed by doctors trained in resuscitation. Full resuscitation equipment must be available and those providing deep sedation should ideally by trained in basic paediatric life support (BPLS) and advanced paediatric life support (APLS).
The use of intravenous sedation can also be hazardous in children as the margin between sedation and anaesthesia is very narrow. Therefore, standards of monitoring should be that same for deep sedation as they are for anaesthesia. These should include continuous monitoring of heart rate and peripheral oxygen saturation. The use of sedation so deep as to cause loss of protective airway reflexes should be avoided by all but anaesthetists.

Level of Sedation:

Sedation in the ICU varies widely from producing complete unconsciousness and paralysis to being nursed awake yet comfortable. There are many components to the ideal regimen but key elements include recognition of pain, anxiolysis, amnesia, sleep and muscle relaxation.

Table 2. Levels of consciousness when using sedation

Conscious sedation	Medically induced state of CNS depression in which communication is maintained so that the child can respond to verbal command.
Deep sedation	Medically induced state of CNS depression in which the child is essentially unconscious and so does not respond to verbal command.
General anaesthesia	Medically controlled state of CNS depression in which the child is unconscious and in which the protective reflexes and the ability to independently maintain a patent airway is lost.

The dosage of commonly used sedative and analgesic drugs varies widely between patients because of variations in metabolism and pharmacodynamics. A valid method for monitoring sedation would allow sedation to be tailored to the individual.
Any scoring system needs to be simple, rapidly performed, non invasive and most importantly, reproducible. Physiological variables, serum concentrations of drugs and neurophysiological tools such as EEG and CFAM have all been used but are expensive and not without their detractors. For a description of BIS monitoring see the module on monitoring in the ICU.

The best systems are clinically based. Below is the University of Michigan sedation scale which is widely used for children.

University of Michigan Sedation Scale (UMSS)

0	**Awake and alert**
1	**Minimally sedated:** tired/sleepy, appropriate response to verbal conversation and or sound
2	**Moderately sedated:** somnolent/sleeping, easily aroused with light tactile stimulation or a simple verbal command
3	**Deeply sedated:** deep sleep, rousable only with significant physical stimulation
4	**Unrousable**

Voepel-Lewis T et al Anesthesiology 2004;101:A1425

The score should be completed regularly by the point of care nurse and reduced in frequency as the patient stabilises. It is suggested levels 1 to 3 can be considered suitable for patients in the ICU.
An increase in the sedation score must prompt the physician to make a differential diagnosis between over sedation or decreased conscious level due to neurological/biochemical disease. As a rule, the aim for the majority of patients is for them to be sleepy, although easily rousable and hence cooperative. It is preferable to allow the patient to breathe as soon as possible on SIMV or triggered ventilation, such as pressure support. Deep sedation with or without paralysis is reserved for severe head injury and when critical oxygenation is required (reduces work of breathing and improves chest compliance).

Antihistamines
Antihistamines are classed as sedating and non-sedating according to their potential for CNS depression. The sedating antihistamines include trimeprazine and promethazine; both are more sedating than chlorpheniramine and cyclizine. Sedating antihistamines have significant anti-muscarinic activity and should not be used in neonates or older children with glaucoma.
Trimeprazine 2-4mg/kg po (Vallergan) is a commonly used sedative in children.

Chloral and Triclofos
Chloral only has sedative properties. It is dependent upon enteral absorption and hence has to be given orally or rectally; occasionally rectally is the preferred route due to the bitter taste of chloral. Chloral is a relatively safe drug but in toxic doses can cause hypotension and apnoea. It is metabolised in the liver to trichlorethanol which is the active agent. It is then further metabolised to trichloracetate and trichlorethanol glucuronide which depend upon renal excretion. The half-life in neonates is 8-66hours. Chloral can cause gastric irritation and hence Triclofos is the preferred agent on PICU.
Dose Chloral: 20 – 50 mg/kg PO tds or qds (max single dose 1g)

Triclofos causes less gastric irritation and like Chloral only has hypnotic properties.
Dose Triclofos: 30 – 50 mg/kg PO qds.

Benzodiazepines
The most commonly used drugs for sedation are benzodiazapines. They are anxiolytic, anticonvulsant and sedative. They have **no** analgesic activity. Their main site of actions are in the limbic and reticular activating system. They act by facilitating gamma amino butyric acid (GABA) the main inhibitory neurotransmitter in the central nervous system. GABA normally opens chloride channels, hyperpolarise neurones and decrease their excitability. Benzodiazapines facilitate GABA by increasing the frequency of the chloride channel opening. They have some cardiorespiratory depressant effects and are also synergistic with opioids. However rapid bolus doses can cause both hypotension and respiratory arrest.

Because of their lipid solubility benzodiazapines have a large volume of distribution; they are metabolised in the liver. Renal excretion is not an important route of elimination. For some benzodiazapines the production of active metabolites and enterohepatic recirculation prolongs their duration of action. The active metabolite of Diazepam is methyldiazepam which results in a half-life of up to 100 hours.
There is wide inter-patient variability in the potency, efficacy and pharmacokinetics of benzodiazepines so the dose must be titrated to the level of sedation.
After long term administration the dose should be ideally reduced gradually or a lower dose reinstated if there is withdrawal (symptoms include insomnia, anxiety, dysphoria and sweating.)
Probability of withdrawal approaches 100% after infusion of Midazolam lasting > 9 days
Oral benzodiazepines are often necessary after prolonged administration of iv preparations. Try Diazepam 0.25 mg/kg bd. Clonidine is also useful in this situation. Give 4-8 mcg/kg/day in three divided doses. A seven day course is recommended[14]

Table 3. Half-lifes for commonly used benzodiazapines

Drug	Half life (h)	Active Metabolites
Diazepam	20-90	Yes
Lorazepam	10-20	No
Midazolam	2-4	No
Temazepam	2-4	No

Midazolam

This agent is probably the most commonly used benzodiazapine in the last 15 years and is still the drug of choice in combination with morphine to provide sedation and analgesia on the PICU. Respiratory depression can occur if given in excess or too rapidly. It also has a more potent cardiodepressant effect when given as a rapid bolus. Withdrawal symptoms can occur after modest duration of use. Its advantage is that it has a number of routes of administration which has given it an important role in the acute treatment of seizure disorders. However it has an extremely bitter taste and causes nasal irritation, this has limited its acceptability.

Midazolam is water soluble at pH 4 yet fat soluble at pH 7 thus avoiding the unnecessary solvents required with the other 2 drugs (diazepam and lorazepam) and hence causing less irritation at the injection site. It has 3 metabolites, one of which (1-hydroxymidazolam) can accumulate in the critically ill. The normal elimination half life is 2 hours but can be as long as a few days in the long term sedated, critically ill patient.

Dose for infusions: 2 – 10 mcg/kg/min

Table 4. Dose and route of administration for midazolam

Route	Dose (mg/kg)	Max dose (mg)
Oral	0.5-0.7	20
Rectal	1.0	20
Nasal	0.2-0.4	10
Sublingual	0.2	10
Intravenous	0.1-0.2	2

Lorazepam

Produces less sedation than midazolam and has a longer duration of action. Can be used on the ICU in place of midazolam infusions in intermittent intravenous boluses or can be given by infusion. Lorazepam also important in treatment of status epilepticus (see Status Epilepticus protocol).

Dose 0.05 – 0.1 mg/kg iv as required.

Its metabolism does not require the P450 system so its administration is less likely to be affected by concurrent drug administration or hepatic failure.

Lorazepam can be used by infusion but some recent reports have raised concern about propylene glycol toxicity (its diluent)[12,13].

Benzodiazapine Antagonists

Flumazenil is a specific benzodiazapine antagonist. Flumazenil is given intravenously and should be given in small aliquots as large doses can precipitate seizures, cardiac arrythmias and acute withdrawal symptoms. It has a half-life of only 1 hour so may need to be given as an infusion or the actions of the benzodiazepines can recur.

Less commonly used medications for sedation:

a. **Phenothiazines**

Phenothiazines have potent central anticholinergic sedative effects. Also produce drying of secretions and has antiemetic properties. It produces sedation 30-40 minutes., particularly as a pre-medication.

b. **Butyrophenones**

Potent sedatives which act on various neurotransmitters including dopamine and noradrenalin. Similar effects to phenothaizine but not commonly used in children.

Medications no longer used or used rarely:

a. **Etomidate**: Historically was used in ICU as an infusion but is now no longer used as it has been shown to cause adrenal suppression, even after a single dose.

b. **Propofol**: Whilst being the mainstay of sedation in adult intensive care there have been an increasing number of reports of deaths using continuous infusion of propofol in children. The adverse effects were metabolic acidosis, cardiac failure, rhabdomyolysis, hyperlipidaemia and hepatomegaly; these were seen particularly in young children on infusions for more than 3 days using doses > 5 mg/kg/hour. It appears that one mechanism may be a deficiency of mitochondrial oxidatative processes possibly

induced by a dialyzable substance, perhaps a propofol metabolite [11].Hence, the Committee on Safety of Medicine in September 2002 advised against the use of propofol in children under 17 years of age as continuous infusion. It should therefore **not** be used as a sedative agent on the PICU. It can occasionally be used in single doses for procedures in older children, but only after discussion with a consultant (this is different from the use of propofol in the anaesthetic room).

Table 5. Guidelines for route of administration, bolus and infusion doses of commonly used sedative agents in children

Drug	Route	Dosage
Diazepam	IV	Bolus: 0.2-0.4mg/kg Infusion: NOT recommended
Midazolam	IV	Bolus: 0.1-0.2mg/kg Infusion: 1-4 μg /kg/min
Flumazenil	IV	Bolus: 5mcg/kg stat, repeat every 60s to max 40 μg /kg
Morphine	IV	Bolus: 0.1 - 0.2mg/kg Infusion: 20-80 mcg /kg/hr
Chloral hydrate	Oral	30 - 50 mg/kg PO 6-8hrly
Trimeprazine	Oral	2-4mg/kg 6-8hrly
Triclofos	Oral	30 – 50 mg/kg PO tds/qds.
Ketamine	IV	Bolus: 1-2mg/kg Infusion: 4 mg /kg/min
Lorazepam	IV	Bolus: 0.05 - 0.1 mg /kg iv prn
Fentanyl	IV	Infusion: 2-3 mg /kg/hr

Barbiturates

One of the oldest class of agents used for sedation, and largely replaced by benzodiazepines. These drugs globally depress the CNS to various degrees and produce effects ranging from sleep and sedation (low doses) to general anaesthesia (high doses). Caution when giving to patients with pain because in small doses they increase the perception of pain and cause excitement rather than sedation (antanalgesic). When barbiturates are given in high doses sufficient to cause general anaesthesia pain perception, in addition to consciousness is obliterated. All are potent anticonvulsants and can be used acutely and chronically for this use. Barbiturates must be given cautiously to haemodynamically unstable patients because they all directly depress the myocardium and the arterial vascular tree and cause significant hypotension. Thiopentone and phenobarbitone are probably the most commonly used.

Thiopentone

Thiopentone has been used especially in the management of patients with severe head injuries with raised ICP and intractable seizure disorders. It causes significant cardiovascular depression and will accumulate during infusions leading to prolonged recovery times. The half life of thiopentone is 12 – 18 hours. The solution is highly alkaline and extravasation causes severe tissue necrosis and pain. It is hepatically metabolized and will accumulate faster in liver failure. Thiopentone is used on PICU in children with severe head injury and high ICP uncontrolled by any other medical or surgical intervention. There is no evidence that its use improves outcome but the theoretical advantage comes from the lowered CNS metabolism. The infusion should be titrated with continuous EEG monitoring to achieve burst suppression. Electrical silence offers no further advantage and leads to increased numbers of complications. Thiopentone is also used in intractable seizures when other medications have proven ineffective. Again its use should be titrated against EEG monitoring to achieve burst suppression before lightening the infusion some 4 – 6 hours later.

Thiopentone is used in RSI (see Anaesthesia module).

Side effects: arrhythmias, myocardial depression, laryngeal spasm, cough, sneezing, rash, hypotension.

Dose: Child > 1 month 5mg/kg iv followed by infusion 2 – 8 mg/kg/hr adjusted according to response.

Ketamine

This agent produces dissociate anaesthesia. It has profound analgesic, amnesic and sedative properties. Low doses (0.5 – 1 mg/kg) provide sedation and analgesia of the skin, muscle and

bone whereas higher doses (1 – 2 mg/kg) produce general anaesthesia. Ketamine acts at the N-methyl-D-aspartate (NMDA) receptor. In low doses the airway reflexes are preserved.
There is a high incidence of extraneous muscle movements; also cardiovascular stimulation and arterial blood pressure may rise with tachycardia (***do not*** use in tricyclic overdose). One of the main disadvantages of ketamine is the incidence of hallucinations, nightmares and other transient psychotic sequelae; these can be reduced by concomitant use of a benzodiazepine.It can cause excess salivation which should be expected. It appears not to accumulate and has bronchodilator properties and is the agent of choice to provide sedation in children with status asthmaticus. New evidence suggests that the traditional view of increase in intracranial pressure with use of Ketamine is not founded on evidence and it is perfectly safe to use it as an induction agent in patients with head trauma[12].

Muscle Relaxants

In some patients on ICU muscle relaxation may be needed in addition to sedation and analgesia. Such indications include:

- Muscle relaxants relax the vocal cords and allow the passage of a tracheal tube
- Early resuscitation (including intubation)
- Refractory hypoxaemia e.g ARDS - will decrease oxygen consumption and optimise chest wall compliance
- During patient transfer
- To allow inverse ratio/prone ventilation or oscillatory ventilation (in some patients).
- Facilitation of procedures
- Risk of barotrauma (high pressure ventilation or poor synchronisation)
- Management of neurosurgical or head injured patients
- Stop spasm of tetanus

Monitoring with a peripheral nerve stimulator is helpful: ablation of more than 3 twitches out of a train of four is unnecessary.

Vecuronium 0 - 6 mcg/kg/min is the preferred drug for continuous muscle relaxation.
It is vital to remember that relaxants have no effect on conscious level or comfort and should be avoided if possible. There are no standard clinical techniques to monitor conscious level in the paralysed patient so it is necessary to give generous doses of sedative drugs. Use of relaxants has fallen from about 90% of patients in the 80's to < 10% of patients in the 00's in the UK. Use has declined since synchronised modes of ventilation have become available.

Non-depolarising muscle relaxants:

- Also known as competitive muscle relaxants these compete with acetylcholine for receptor sites at the neuromuscular junction.
- Their action may be reversed by anticholinesterases such as neostigmine.
- Divided into 2 groups:
  - Aminosteroid: pancuronium, rocuronium, vecuronium.
  - Benzylisoquinolinium group: atracurium, cisatracurium, mivacurium.
- ND muscle relaxants have a slower onset of action than suxamethonium.
- Not considered to be triggers for malignant hyperthermia
- Benzylisoquinolinium ND muscle relaxants are associated with histamine release which can cause skin flushing, hypotension, tachycardia, bronchospasm.
- Most aminosteroid ND muscle relaxants cause little or no histamine release.

Doses Non-depolarising Neuromuscular blockers

- Atracurium 0.5mg/kg or infusion 0.2 – 0.4 mg/kg/hr
- Cis-atracurium 0.2mg/kg
- Vecuronium 0.2mg/kg or infusion 0.1 – 0.2 mg/kg/hr
- Pancuronium 0.2mg/kg
- Rocuronium 0.5mg/kg

Depolarising Neuromuscular blockers

Suxamethonium has the most rapid onset of action of any of the muscle relaxants and is ideal if fast onset and brief duration of action are required, for example for intubation. Duration of action is about 2 – 6 minutes following intravenous dose of 1mg/kg. Neonates and young children are less sensitive and a higher dose may be required – typically 2 mg/kg.
Suxamethonium acts by mimicking acetylcholine (Ach) at the NMJ but hydrolysis is much slower than for Ach; depolarisation is thereby prolonged resulting in neuromuscular blockade. Its action cannot be reversed and recovery is spontaneous (if neostigmine is given it will *potentiate* this block). Bradycardia is a frequent occurrence with suxamethonium use and concomitant use of atropine reduces this and the excessive salivation which also occurs. Prolonged paralysis may be seen in patients with low or atypical plasma cholinesterase.
Suxamethonium can cause a rise in serum potassium which makes it inappropriate for use in cases of renal failure. Excessive potassium release also occurs after 48hrs in extensive burns and spinal cord injury.
Contraindications: family history of malignant hyperthermia, hyperkalaemia, burns, prolonged immobilisation, myopathies, major trauma.

Muscle relaxation

Agent and action	Indications	Cautions	Dose	Adverse effects
Suxamethonium Depolarising neuromuscular blocker (NB. have Atropine ready)	Rapid sequence intubation Post extubation laryngospasm	Malignant hyperpyrexia Hyperkalaemia Burns Muscle damage Disuse atrophy Airway obstruction	1-2 mg/kg bolus Repeat dose of 0.25 - 0.5 mg/kg with atropine Action at 45-60s, lasts <5mins	Malignant hyperpyrexia Hyperkalaemia Transient rise in IOP and ICP Muscle pain BRADYCARDIA
Atracurium Non depolarising	Muscle paralysis	Airway obstruction Not for rapid sequence Asthma (histamine release)	0.5 mg/kg bolus Infusion 0.2-0.4 mg/kg/hr Half life 20mins (Hoffman degradation)	Bradycardia Hypotension Bronchospasm Urticaria
Vecuronium Non depolarising	Muscle paralysis	Airway obstruction Not for rapid sequence	0.2 mg/kg bolus Infusion as below Duration of action 20-30 min.	Bradycardia Hypotension
Pancuronium Non depolarising	Prolonged muscle paralysis Hypotensive patients	Airway obstruction Not for rapid sequence Renal/hepatic failure Muscle atrophy Tetanus (symptomatic)	0.2 mg/kg iv Not used as infusion Duration of action 1-2h. Causes 20% increase in HR and BP	Tachycardia Hypertension
Rocuronium Non depolarising	Effect within 2 minutes – most rapid onset of action of ND group. Intermediate duration of action	A mild vagolytic effect leads to a slight increase in heart rate and mean arterial pressure. No significant histamine release. Bronchospasm is very uncommon.	600 mcg/kg iv Excreted primarily by hepatic uptake and hepatobiliary excretion. The pharmacokinetics are not significantly altered in renal failure.	expensive

Problems with relaxants

The patient may receive inadequate sedation and be aware. This can be checked by withdrawing muscle relaxants for a time to allow recovery of muscular function and assessment of sedation levels.

- Accumulation especially with aminosteroids in ARF
- Prolonged paralysis after discontinuation from accumulation
- Severe myopathy critcal illness polyneuropathy occasionally (esp. if steroids used as well)
- Loss of protective reflexes
- Tendency to perhaps oversedate
- Enhanced paralysis from other common ICU problems such as hypokalaemia, aminoglycoside antibiotics, hypophosphataemia

Other sources of information:
Websites:

1. **www.gosh.nhs.uk – for pain services, epidurals, NCAs and PCAs**
2. **www.rch.org.au – clinical practice guidelines, see sedation, analgesia.**
3. **www.emedicine.com – for all related topics.**

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Information for Year 2 ITU Training (advanced):

Year 2 ITU curriculum

Physiology:

- Drug therapy influence on nociceptive mechanisms
- Effects of organ system failure on drug elimination.

New agents: e.g. dexmedetomidine

Withdrawal:

- Weaning regimes
- Recognition & management of withdrawal syndromes

Clinical:

- Evaluation of neuromuscular blockade – see "monitoring in ITU" module.

Pain treatment and Perception

A person's response to pain treatment may be due to factors other than the direct effect of analgesics. Amelioration of pain is often associated with modalities that appear to make no scientific sense.

Pain is modulated, enhanced, or diminished by both cerebral and peripheral mechanisms. Cerebral factors include the placebo response, psychological phenomena, and conscious cognitive activation. In addition to evoking endogenous opioids, these central mechanisms activate antinociceptive pathways beginning in the limbic forebrain and relayed in the periaqueductal gray matter to primary afferent nociceptive sites in the spinal cord dorsal horn (and medullary nucleus caudalis). Obvious peripheral factors that may diminish pain perception are those that decrease afferent stimuli. Paradoxically, stimulation of afferent neurons may also ameliorate pain by activating spinal or supraspinal inhibitory mechanisms. Finally, improvement in pain or other symptoms is often falsely attributed to a therapy when remission occurs because the underlying illness has run its normal course.

Effects of other drugs on sedation and analgesia on the ICU

Table 1. Some interactions with thiopentone

Interacting drug	Effect	Mechanism	Management
Diazoxide, salicylates, probenecid	Hypotension	Pharmacokinetic. Competition with barbiturates for plasma protein binding sites	Reduce dose of barbiturate. Treat hypotension with IV fluids
ß-Blockers	Reduced serum ß-blocker concentrations	Pharmacokinetic. Enhanced metabolism by barbiturates	Close monitoring
Monoamine oxidase inhibitors	Hypotension, CNS and respiratory depression	Pharmacokinetic. Interference with biotransformation of barbiturates	Supportive treatment. Consider using regional blocks with local anaesthetics. Titrate dose of barbiturate
Opioids, propofol, benzodiazepines	Potentiation of hypnotic effects and respiratory depression	Pharmacodynamic. Additive or synergistic interaction	Clinically useful. Titrate dose of barbiturate. monitor respiratory function and consider using mechanical ventilation when indicated

Ketamine (subhypnotic doses)	Antagonism of thiopental sodium	Pharmacodynamic	Increase dose of thiopental sodium
Metoclopramide	Decreases thiopental sodium dose requirements	Pharmacodynamic. Dopamine receptor antagonism	May be clinically useful
Adrenergic drugs	Dysrhythmias	Pharmacodynamic	Treat ventricular dysrhythmia with lidocaine (lignocaine)
Suxamethonium chloride (succinylcholine)	Aggregate formation resulting in disseminated intravascular coagulation	Pharmacodynamic	Administer drugs into large veins. Flush tubing with saline between administration of each drug

Table 2. Some interactions with ketamine

Interacting drug	Effect	Mechanism	Management
Halothane, diazepam	Prolonged recovery due to increased plasma concentration and prolongation of elimination half-life of ketamine	Pharmacokinetic. Decreased hepatic clearance of ketamine	Reduce dosages of ketamine and other drugs
Volatile anaesthetics	Reduced cardiac output, hypotension	Pharmacodynamic. Blockade of the indirect cardiovascular stimulant effects of ketamine	Careful monitoring
Thyroxine	Hypertension and supraventricular tachycardia (in 2 reported cases)	Pharmacodynamic	Ketamine should be used cautiously. Treat hypertension if present
Theophylline	Extensor-type seizures (in 4 reported cases)	Pharmacodynamic. Possible reduction in seizure threshold	Maintain theophylline concentration within the therapeutic range
Thiopental sodium (thiopentone sodium)	Subhypnotic doses of ketamine	Pharmacodynamic antagonises thiopental sodium	Higher doses of thiopental sodium may be required
Atracurium	Prolongation of the neuromuscular block	Pharmacodynamic	Monitor neuromuscular function and titrate doses of neuromuscular blocking drugs

3. Morphine Interactions

Generally, effects of morphine may be potentiated by alkalizing agents and antagonized by acidifying agents. Analgesic effect of morphine is potentiated by chlorpromazine. CNS depressants such as anaesthetics, hypnotics, barbiturates, phenothiazines, chloral hydrate, sedatives, MAO inhibitors (including procarbazine hydrochloride), antihistamines, B-blockers (propranolol) and other narcotics may enhance the depressant effects of morphine.

Morphine may increase anticoagulant activity of wafarin and other anticoagulants.
Antibiotics are often used with opioids in patients undergoing medical or surgical procedures. The best documented metabolic interactions are with erythromycin and rifampicin. Erythromycin increases and rifampicin decreases the effects of opioids. Some of the drugs used to treat epilepsy, particularly carbamazepine, phenytoin and barbiturates, can speed up the metabolism of opioids in the liver.

4. Midazolam and BDZ Interactions

Caution is advised when midazolam is administered concomitantly with drugs that are known to inhibit the cytochrome P450 3A4 enzyme system (ie, some drugs in the drug classes of azole antimycotics, protease inhibitors, calcium channel antagonists, and macrolide antibiotics). Drugs such as erythromycin, diltiazem, verapamil, ketoconazole, fluconazole and itraconazole were shown to significantly increase the C_{max} and AUC of orally administered midazolam. These drug interactions may result in increased and prolonged sedation due to a decrease in plasma clearance of midazolam. Although not studied, the potent cytochrome P450 3A4 inhibitors ritonavir and nelfinavir may cause intense and prolonged sedation and respiratory depression due to a decrease in plasma clearance of midazolam. Caution is advised when midazolam syrup is used concomitantly with these drugs. Dose adjustments should be considered and possible prolongation and intensity of effect should be anticipated Cytochrome P450 inducers, such as rifampin, carbamazepine, and phenytoin, induce metabolism and caused a markedly decreased C_{max} and AUC of oral midazolam in adult studies. Although clinical studies have not been performed, phenobarbital is expected to have the same effect.

One case was reported of inadequate sedation with chloral hydrate and later with oral midazolam due to a possible interaction with methylphenidate administered chronically in a 2-year-old boy with a history of William's syndrome. The difficulty in achieving adequate sedation may have been the result of decreased absorption of the sedatives due to both the gastrointestinal effects and stimulant effects of methylphenidate. The sedative effect of midazolam is accentuated by any concomitantly administered medication which depresses the central nervous system, particularly narcotics (eg, morphine and fentanyl), propofol, and ketamine

5. Neuromuscular Blockers

The concomitant use of parenteral antibiotics such asaminoglycosides, tetracyclines, clindamycin, bacitracin, and polymixin B mayintensify the neuromuscular blockade produced by vecuronium. Recurrent paralysis can occur for patients receiving quinidine after vecuronium use. The neuromuscular blocking effect and the duration of action of vecuronium also may be increasedwith the use of other NMBAs or calcium channel blockers. Conversely, the concomitant use of azathioprine or theophylline has beenshown to decrease the neuromuscular blockade of vecuronium.

New Agents

Dexmedetomidine

Dexmedetomidine is a centrally acting alpha-2 adrenergic agonist that is currently approved by the US Food and Drug Administration for short-term use (≤24 h) to provide sedation in adults in the ICU. This drug has been shown to be efficacious in adult medical and surgical patients in providing sedation, anxiolysis, and analgesia. Dexmedetomidine has been associated with rapid onset and offset, hemodynamic stability, and a natural, sleep-like state in mechanically ventilated adults. To date, there are few publications of the use of this drug in children, and prolonged infusion has not been described. Some case reports of use of dexmedetomidine in children exist, which appear to indicate successful use [1-4].

Sucrose

Whilst this is not a new drug there has been a resurgence in interest in its use on the NICU. Oral sucrose has been shown to reduce pain in infants less than three months of age during minor procedures.
Oral sucrose may be given to infants during procedures such as blood collection, IV insertion, eye examination and lumbar puncture.
Sucrose may be more effective if given with a dummy as the dummy promotes non-nutritive sucking which contributes to calming.
Other strategies which assist in calming infants and can be used as an adjunct to sucrose include feeding (if allowed), cuddling, and wrapping.
Other appropriate local or systemic analgesic agents should be administered as required.

Dose[5]:

Maximum 2mL (0.5mL for infants below 1500 grams) administered orally for each procedure.

Two minutes prior to a painful procedure, administer a small amount (around 0.25ml) of sucrose onto the infant's tongue. Offer a dummy if this is part of the infants care.
Continue giving remainder of sucrose slowly during the procedure for a total dose of 2ml, until the procedure is completed. Sucrose is only effective if given orally. There is no effect if given via an oral or nasogastric tube.
The addition of non-nutritive sucking enhances the analgesic effect of sucrose.

Withdrawal

The mechanisms by which opioids cause tolerance and physiological dependence are not firmly established. Proposed mechanisms include changes in the receptors and their binding affinities which may result in negative feedback inhibition of endogenous opioid production; or perhaps neurotransmitter changes in both concentration and function take place.

One theory, gaining popularity, suggests that neuronal firing from the locus coeruleus (LC) increases during dependence and that withdrawal symptoms are a manifestation of excessive noradrenaline release from that region of the brain. In animal models it has been seen that morphine dependence produces changes in the number and intensity of nitric oxide synthase immunoreactive neurons throughout several regions of the brain raising the possibility that NO up regulation at NMDA receptors may cause the excessive noradrenergic hyperacitivity seen in the LC during withdrawal[8].

The signs and symptoms of withdrawal in children occur in a classic triad:

- Neurological excitability
- Gastrointestinal dysfunction
- Autonomic dysfunction

Table. Signs and symptoms of withdrawal

Neurologic Excitability	
Agitation	Inability to sleep
Irritability	Yawning
Crying/inconsolability	Tremors
Increased tone	Hyperactive reflexes
Tachypnea	Seizures
Sneezing	Uncoordinated suck
Gastrointestinal dysfunction	
Vomiting	Abdominal pain
Diarrhea	Dehydration
Feeding intolerance	Poor weight gain
Autonomic dysfunction	
Tachycardia	Pupillary dilatation
Fever	Sweating
Itching	

Buck M. Pediatric Pharmacotherapy 2000 July 6(7).

In 1994 Katz et al found that of 23 infants and children given fentanyl by continuous infusion while mechanically ventilated, 57% developed dependence; dose and duration of use being positive predictors of dependence[9]. Scott et al surveyed medical staff on ICUs in 1995 and found that 74% thought that managing dependence was a real problem[10]. Many regimes for managing withdrawal have been proposed:

- Gradual tapering of opioid therapy (most widely used)
- Substitution of other agents to control symptoms

The tapering of therapy often involves conversion to oral agents to facilitate discharge from ICU. There has been a recent increase in the use of methadone to aid this; it has several theoretical advantages including a relatively high oral bioavailability, along elimination half life and an oral liquid form.
There have been a number of paediatric studies looking at the use of methadone in children and it has been found to be efficacious in the treatment of pain[11,12]. Berde et al conducted a randomized double blind study to compare methadone iv with morphine iv for postoperative pain

in children. They found the two agents equally effective but the methadone group needed fewer supplemental doses.

A tapering regime using methadone[8]:

Child on opioid for > 5 – 7 days continuously, then discontinuation by weaning advisable
Reduce dose by 10% every 12 to 24 hours, depending on the patient's condition.
If the patient shows signs of withdrawal then increase the dose to the previous amount at which the patient was comfortable and stop the tapering process for 24 hours.
When substitution with an oral agent is required, methadone may be started at 0.05 to 0.1 mg/kg.
Administration of drug is required every 6 hours initially to provide accumulation (24 – 48 hrs).
After this period the dosing interval can be lengthened to every 12 to 24 hours; during this period the intravenous agent should be gradually discontinued.
Once the patient is stable the methadone dose may be tapered by 5 – 10 % every 24 to 48 hours as tolerated.
Do not calculate equivalent methadone: morphine dose as range variability for equipotency is too high. Many patients on high dose morphine or fentanyl will be adequately treated with only moderate doses of methadone.
Methadone may be a useful drug for withdrawal but some authors have raised concerns regarding its effect on prolongation of the QT_C on the ECG[17].
Patient Assessment: must be ongoing during tapering process. Several scoring systems which convert symptoms into a numeric score for comparison are in use. One of earliest and most reproducible is the Neonatal Abstinence score developed by Finnegan[13]. It was designed for the evaluation of neonates born to drug addicts. Using 31 items, it allows a semi quantitative measure of the degree to which the newborn is experiencing symptoms of withdrawal. This scale can also be used to assess the resolution of signs and symptoms after initiating treatment. To obtain a daily average score, measurements are performed every 4 hours until the patient is stable. If 3 consecutive scores are equal to or greater than 8, treatment for withdrawal is started. These scoring systems have now been adopted for use in patients of all ages with iatrogenic dependence.

Adjunctive therapies:

Clonidine is used as a morphine sparing agent and in the management of withdrawal (as described above). It is thought to act on the LC by decreasing the firing rate of noradrenergic neurons. Like other agents substituted for opioids to control symptoms of withdrawal, such as barbiturates, clonidine may not ameliorate all symptoms of withdrawal and they are best used in conjunction with a tapering system.

Substitution therapies;

One study by Hiroaki et al.[14] looked at the substitution of ketamine for opioid and benzodiazepine infusion rather than using a tapering regime. This was only in one paediatric patient (2yrs old)and was after several failed attempts at tapering the drugs. There was however a sound rationale for this regime. Ketamine is a noncompetitive NMDA receptor antagonist and it has been shown that NMDA receptor antagonists attenuate the occurrence of opioid dependence and withdrawal in adult humans[15]. The effects of NMDA receptor antagonists is not known in children and indeed in neonatal rats the receptors are functionally immature so there is likely an age dependent cut off for the effect – the exact level for this is unknown. This may be an area for further research.

Other ways to reduce withdrawal:

Patients who require mechanical ventilation are commonly given a continuous infusion of sedatives to reduce their anxiety, prevent agitation, decrease oxygen needs, and facilitate nursing care. Continuous infusion of these drugs has become standard practice because it maintains consistent levels of sedation and improves patient comfort. One drawback, however, is that continuous infusion can lead to drug accumulation, delay re-awakening and cause dependence. Sedation breaks have been used on adult ICUs as a way of reducing the incidence and severity of opiate and benzodiazepine withdrawal.
A study by Kress et al in 2000 reported in the NEJM[16], looked at 128 patients receiving sedation and analgesia on the ICU all of whom were mechanically ventilated. Kress and colleagues suspected that a brief daily sedative interlude could prevent drug build-up and decrease related problems yet maintain patient comfort.
They performed a randomized, controlled trial involving 128 critically ill adult patients who required mechanical ventilation. Half of the patients received continuous infusions of sedatives, which were discontinued at the discretion of the ICU team.

The other half had their sedative and morphine infusions stopped each day until the patient either woke up enough to follow simple commands (such as "open your eyes" or "squeeze my hand") or began to show signs of agitation or discomfort. Patients who still needed sedatives were then restarted on continuous infusion, although they were often given a lower dose.
The 68 patients who had daily sedative breaks recovered much more quickly. They were able to breathe on their own 33 % sooner median of 4.9 days, compared to 7.3 days for those who did not have sedative breaks. They left the ICU 35 % sooner, after a median of 6.4 days, compared to 9.9 days.
Patients who had their sedatives stopped daily were nearly 10 times more likely to spend some portion of each day awake, which made assessment of mental status changes much easier. The 60 patients receiving continuous sedatives required 16 diagnostic tests related to mental status (13 brain CT scans, two brain MRI scans, one lumbar puncture), most of which were not helpful compared to six brain CT scans in the 68 patients who had a daily sedative recess.
Although this study was too small to provide statistically convincing evidence, patients who had their sedatives interrupted did show a trend toward better outcomes, with 10 percent fewer deaths, fewer patients sent to long-term ventilator facilities, and 59 percent of patients discharged to home, compared to only 40 percent of the patients given continuous sedatives. The average length of hospital stay was also shorter, 13.3 days compared to 16.9.
These studies have not yet been repeated in children and may be more difficult to do as children can wake more abruptly and for younger children it may be difficult to reason with them increasing the possible incidence of extubation and line removal. However any technique which can move towards reduced withdrawal, length of stay, VAP must be desirous and sedation break regimes should be worked towards.

Other sources of information:

Websites.

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Appendix 1

Modified TPPPS

		Score
1	*Verbal expression of pain*	
	Verbal pain complaint—any word, phrase or statement that refers to pain, hurt or discomfort.	
	Examples: "It hurts", "Ow", "Oh", "You're hurting me".	
2	*Cry*—tears in the eyes or running down the face and/or making sobbing sounds.	
	Examples: sobbing, tears in the eyes, tears falling down cheeks.	
3	*Groan, moan, grunt*—deep, low-pitched vocalisations expressing pain, hurt or discomfort.	
	Examples: non-intelligible, low-pitched sounds. May be drawn out (moan) or abrupt (grunt).	
4	*Scream*—acute, loud, high pitched cry.	
	Examples: sharp, shrill, harsh, high-pitched vocalisation, shriek.	
5	*Facial expression of pain*	
	Open mouth, lips pulled back at corners—open mouth, lips pulled back at corners with a downward pull on the jaw.	
6	*Squint/close eyes*—eyelids taut, stiff, closed or nearly closed with wrinkling of the skin at the lateral aspect of the eyes.	
7	*Brow bulge/forehead furrow*—bulging, creasing, or furrows above and/or between the eyebrows.	
8	*Bodily expression of pain*	
	Restless motor behaviour—rub/touch painful area, or unrestrained activity. May appear random or to lack goal direction. The body and/or head is never still.	
	Examples: twisting and turning of torso and/or head while lying down, flailing of arms and/or legs, arching, repetitive fine motor activity. Child touches incisional area, iv site.	

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Annexure A: COMFORT Score

Patient Name:	**Weight:**													**Daily Target Score=**
Date	Score													
Alertness														
Deep asleep	1													
Lightly asleep	2													
Drowsy	3													
Fully Awake/alert	4													
Hyper-alert	5													
Calmness/Agitation														
Calm	1													
Slightly Anxious	2													
Anxious	3													
Very Anxious	4													
Panicky	5													
Physical Movement														
No movement	1													
Occasional, slight movement	2													
Frequent/slight movements	3													
Vigorous movements limited to extremities	4													
Vigorous movements involving torso and head	5													
Muscle Tone														
Muscles totally relaxed	1													
No muscle tone	2													
Normal muscle tone	3													
Increased muscle tone and flexion of fingers/toes	4													
Extreme muscle rigidity and flexion of fingers/toes	5													
Facial Tension														
Facial muscles totally relaxed	1													
Facial muscle tone relaxed, no facial muscle tension evident	2													
Tension evident in some facial muscles	3													
Tension evident through facial muscles	4													
Facial muscles contorted and grimacing	5													
Crying (non-ventilated patient)														
Quiet breathing, no crying sounds	1													
Occasional sobbing or moaning	2													
Whining (monotone)	3													
Crying	4													
Screaming or Shrieking	5													
Respiratory response (Ventilated patient)														
No coughing and no spontaneous respiration	1													
Spontaneous respiration with little or no response to ventilation	2													
Occasional cough or resistance to ventilator	3													
Actively breaths against ventilator or coughs regularly	4													
Fights ventilator, coughing or choking	5													
Heart Rate Baseline=														
Heart rate below baseline	1													
Heart rate consistently at baseline	2													
Infrequent elevations of more than 15% from baseline or 1-3 episodes/hr	3													
Frequent elevations of 15% from baseline or more than 3 episodes/hr	4													
Sustained elevations of more than 15% of the baseline	5													
Blood Pressure Baseline MAP=														
Blood Pressure below baseline	1													
Blood Pressure consistently at baseline	2													
Infrequent elevations of more than 15% from baseline or 1-3 episodes/hr	3													
Frequent elevations of 15% from baseline or more than 3 episodes/hr	4													
Sustained elevations of more than 15% of the baseline	5													
Total Comfort Score														
Action Taken														
Initials														
Key: B- Bolus, D- Decrease infusion, I- Increase infusion, N- No action, O- other														

Observe the child each hour for 2 minutes (guidance notes attached). Assess the muscle tone at the end of 2 minutes by gently touching the child. Levels of sedation:

1. 8-16 points: deep sedation
2. 17-26 points: optimal sedation
3. 27-40 points: inadequate sedation