

Postoperative analgesia in infants and children

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Over 20 yr ago, a survey reported that 40% of paediatric surgical patients experienced moderate or severe postoperative pain and that 75% had insufficient analgesia.¹⁰⁶ Since then, a range of safe and effective techniques have been developed.

Neonatal pain perception

The structural components necessary to perceive pain are already present at about 25 weeks gestation whereas the endogenous descending inhibitory pathways are not fully developed until mid-infancy.^{2,4,164} Opioid and other receptors are much more widely distributed in fetuses and neonates.^{52,53,62,66,127} Fetuses subjected to intrauterine exchange transfusion with needle transhepatic access will show both behavioural signs of pain as well as a hormonal stress response.⁶⁴ Significant pain stimulation without proper analgesia, for example circumcision, will not only cause unacceptable pain at the time of the intervention but will produce a 'pain memory' as illustrated by an exaggerated pain response to vaccination as long as 6 months following the circumcision.^{148–150} Both neonates and infants are able to mount a graded hormonal stress response to surgical interventions and adequate intra- and postoperative analgesia will not only modify the stress response but has also been shown to reduce morbidity and mortality.^{1,3,5,6,16,17,163,167}

Successful postoperative pain management in infants and children

A pragmatic, practical approach to paediatric postoperative pain management has been developed and used in recent years in most paediatric centres. Realistic aims are to recognize pain in children, to minimize moderate and severe pain safely in all children, to prevent pain where it is predictable, to bring pain rapidly under control and to continue pain control after discharge from hospital.^{108,109,117,119,125}

Prevention of pain whenever possible, using multi-modal analgesia, has been shown to work well for nearly all cases and can be adapted for day cases, major cases, the critically ill child, or the very young. Many acute pain services use

techniques of concurrent or co-analgesia based on four classes of analgesics, namely local anaesthetics, opioids, non-steroidal anti-inflammatory drugs (NSAIDs), and acetaminophen (paracetamol).^{61,72,74,97,98,117,119,135} In particular, a local/regional analgesic technique should be used in *all* cases unless there is a specific reason not to and the opioid-sparing effects of local anaesthetics, NSAIDs, and acetaminophen (paracetamol) are useful. Indeed, for many day-case procedures, opioids may be omitted because combinations of the other three classes provide good pain control in most cases.^{88,125} Regional anaesthesia is nearly always conducted in *anaesthetized* children, but some high risk neonates have lower perioperative morbidity after inguinal surgery when *awake* spinal anaesthesia is used.^{91,161}

An individualized pain management plan⁷² can be made for each child based on a cycle of assessment and documentation of the child's pain using appropriate tools and self-reporting, with interventions linked to the assessments.^{30,60,63} A safety net is needed for rapid control of breakthrough pain, to monitor the efficacy of analgesia, to identify and treat adverse effects, and to ensure equipment is functioning correctly.¹¹⁶

In paediatric hospitals or other centres with significant numbers of paediatric surgical interventions, the establishment of a dedicated paediatric pain service is the standard of care. Where this is not possible, adult pain services often manage children with specific paediatric medical and nursing advice and expertise. In other settings substantial improvement is possible by the establishment of clinical routines and protocols for the assessment and treatment of paediatric postoperative pain. A network of nurses with a special interest in paediatric pain management can form the basis for continuous education. A well-structured protocol for postoperative analgesia with clear instructions for parents is essential following paediatric day-case surgery.^{118,124,125,165}

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Local and regional anaesthesia

Benefits associated with the use of paediatric regional anaesthesia

Regional anaesthesia produces excellent postoperative analgesia and attenuation of the stress response in infants and children.^{22 43 48 139 166 167} Epidural anaesthesia can decrease the need for postoperative ventilation after tracheo-oesophageal fistula repair,²⁶ and reduce the complications and costs following open fundoplication.^{110 162}

Safety aspects of paediatric regional anaesthesia

A large prospective 1-yr survey of more than 24 000 paediatric regional anaesthetic blocks found an overall incidence of complications of 0.9 in 1000 blocks, with no complications of peripheral techniques.⁶⁵ Complications were transient and half were judged to have been caused by the use of inappropriate equipment. The commonest problems with paediatric regional anaesthesia are technical: either failure to establish a block or failure of maintenance of the block. Infection, pressure area problems, peripheral nerve injury, local anaesthetic toxicity, and serious adverse effects of opioids are much rarer.⁴² A large 5-yr prospective audit of 10 000 paediatric epidural catheter techniques is currently taking place in the UK to try to establish the relative risk of these problems in modern practice.

Some simple local anaesthetic techniques for postoperative analgesia

Local anaesthetic gel topically applied to the site of circumcision, and instilled onto or infiltrated into small open wounds are simple, safe, and effective techniques.^{7 56 135} Wound perfusion can also be particularly useful for iliac crest bone graft donor sites (used for alveolar bone grafting in some techniques of cleft palate repair).¹¹⁹ Dressing perfusion by applying dilute local anaesthetic onto a foam layer applied to skin graft donor sites is also simple, very effective and safe provided the maximum dosage limits are strictly adhered to. These sites can otherwise be extremely distressing to the child for a period up to 48 h.¹¹⁹

Recent developments in regional analgesia

Descriptions of the technical aspects of regional anaesthesia and management of the child with regional block are readily available.^{35 41 119 121 124 130} Pharmacokinetics of local anaesthetics in infants and children have been comprehensively reviewed recently.¹⁰⁷

Spread of epidural dye

Radiological assessment of contrast injected through epidural catheters in babies (1.8–4.5 kg) after major surgery found that both the quality and extent of spread were different for every baby. Filling defects and ‘skipped’ segments were common. Spread was more extensive after 1 ml kg⁻¹ compared with 0.5 ml kg⁻¹ (mean 11.5 [3.03] vs 9.3 [3.68]

segments, $P=0.014$) (but not twice as great) with fewer ‘skipped’ segments and greater density of dye.¹⁵⁸

Confirming the tip position of catheters threaded from the sacral hiatus

The technique of threading catheters from the sacral hiatus to position the tip at thoracic or lumbar level²⁴ reported success rates of 85–96%, particularly in small children. A retrospective review of radiographs in babies younger than 6 months of age¹⁵⁶ found that only 58 catheter tips were considered optimal (67%); 10 were too high (12%); and 17 were coiled at the lumbosacral level (20%). Some units use radiological screening routinely but for many others this is not feasible. An alternative approach using electrocardiography has been described.¹⁵³ A specially devised catheter enables display of the electrocardiograph (ECG) signal from the tip and this is compared with the ECG from a surface electrode positioned at the ‘target’ segmental level. When the ECG traces are identical, the tip of the catheter is at the target level. In a descriptive study of 20 children aged 0–36 months, the authors were able to position all the tips to within two vertebral spaces of the target levels (either T4, T7, or T10). In contrast to their previous method of using stimulating epidural catheters and evaluating muscle contractions,¹⁵⁴ the technique can be used after administration of neuromuscular blocking agents or epidural local anaesthetics. However, neither of the two techniques described by Tsui^{153 154} will exclude a catheter lying at the appropriate segmental level but in the subarachnoid space or intravascularly.

Ultrasonography-guided regional anaesthetic techniques

Ultrasonography allows real-time visualization of anatomical structures, guides the blocking procedure itself, and shows the spread of the local anaesthetic solution injected. A more rapid onset of block using less local anaesthetic solution is particularly attractive for paediatrics where most blocks are sited in anaesthetized patients. Ultrasound guidance can also be helpful for caudal and epidural blocks in infants and children as the sacrum and vertebrae are not fully ossified.^{33 103} Ultrasound-guided techniques have been described for infraclavicular brachial plexus blockade,⁸⁶ and lumbar plexus block in children.¹⁰³

Surface mapping of peripheral nerves with a nerve stimulator

Nerve mapping using a nerve stimulator is helpful for teaching peripheral nerve and plexus blocks in the upper and lower limbs, and in patients where the surface landmarks are obscure or distorted.²⁷

Use of continuous peripheral nerve blocks

Continuous catheter techniques are becoming popular in children for femoral, brachial plexus, fascia iliaca, lumbar plexus, and sciatic blockade.^{37 39 40 82} Disposable infusion devices can be used as an alternative to standard infusion equipment.³⁸

Table 1 Suggested maximum dosages of bupivacaine, levobupivacaine, and ropivacaine in neonates and children. The same dose is recommended for each drug

Single bolus injection	Maximum dosage
Neonates	2 mg kg ⁻¹
Children	2.5 mg kg ⁻¹
Continuous postoperative infusion	Maximum infusion rate
Neonates	0.2 mg kg ⁻¹ h ⁻¹
Children	0.4 mg kg ⁻¹ h ⁻¹

Choice of local anaesthetic solution

A large safety study has established safe-dosing guidelines for racemic bupivacaine in children (Table 1) and this has greatly reduced the incidence of systemic toxicity.^{19,169} Racemic bupivacaine is gradually being replaced by ropivacaine or levobupivacaine. This change is driven by the reduced potential for systemic toxicity and the lower risk of unwanted motor blockade. There are now sufficient paediatric data to recommend either of the new agents.^{25,31,44,78,79,80,81,82,95,120,133,151,170} Bosenberg has reported non-toxic plasma concentrations of ropivacaine following a dose of up to 3 mg kg⁻¹ for ilioinguinal blockade,^{23,28} but 3.5 mg kg⁻¹ for fascia iliaca compartment blockade has been reported to cause potentially toxic plasma concentrations, namely 4–5 µg ml⁻¹.¹²⁹ Thus, the reduced risk of systemic toxicity should not persuade anaesthetists to exceed the previous dosing guidelines for racemic bupivacaine. For continuous epidural levobupivacaine, the use of a 0.0625% solution appears optimal for lower abdominal or urological surgery.⁹⁵ For single injection caudal blockade, ropivacaine and levobupivacaine provide similar postoperative analgesia compared to racemic bupivacaine with slightly less early postoperative motor blockade,^{36,49,80} and with no discernible differences between ropivacaine and levobupivacaine.^{49,79,80} The esterase systems in tissues, plasma, and red blood cells are mature in early life, and ester local anaesthetics such as amethocaine (tetracaine) and 2-chloroprocaine are particularly applicable in neonates.^{18,93,99,160}

Adjuncts to local anaesthetics

A recent systematic review of paediatric caudal adjuncts has been published.¹³ Caution is required in neonates as sedation and apnoea have been noted. In a survey of the UK members of the Association of Paediatric Anaesthesia, 58% of respondents stated that they used adjuvants with local anaesthetics for caudal epidural blockade in children to prolong the duration of analgesia without increasing side-effects such as motor blockade. The commonest were ketamine 32%, clonidine 26%, fentanyl 21%, and diamorphine 13%.¹⁴⁰ Although preservative-free racemic ketamine is a very effective agent,^{34,126} preservative-free S(+)-ketamine is more potent and may reduce neuro-psychiatric effects.⁸⁷ Caudally administered S(+)-ketamine (1 mg kg⁻¹) as the sole agent has even been reported to produce similar postoperative analgesia to bupivacaine 0.25% with

epinephrine.¹⁰⁴ The main action of adjunct ketamine is most likely mediated by actions on spinal *N*-methyl D-aspartate (NMDA)-receptors, as the same dose given systemically produces a much shorter duration of analgesia.¹⁰⁵ When used for single injection, S(+)-ketamine has been found to be more effective in prolonging postoperative pain relief than clonidine.⁵⁰ The combination of S(+)-ketamine 1 mg kg⁻¹ and clonidine 1 µg kg⁻¹ without the concomitant use of local anaesthetics for caudal blockade produced approximately 24 h of adequate postoperative analgesia compared with only 12 h for plain S(+)-ketamine.⁶⁸ Adjunct clonidine in the dose range of 1–2 µg kg⁻¹ for single injection caudal blockade will typically double the duration of analgesia compared with plain local anaesthetics,^{83,94} and addition of approximately 0.1 µg kg⁻¹ h⁻¹ will enhance the effect of continuous epidural blockade.⁵¹ Recent data suggest that the systemic effect of clonidine might be more important than the local action.⁶⁹ The routine use of opioids as additives for postoperative analgesia has recently been critically challenged.¹⁰⁰ Although there is a risk of respiratory depression, less dramatic side-effects such as itching, nausea and vomiting, urinary retention, and decrease gastrointestinal motility are more troublesome.^{47,98} A recent comparison of plain levobupivacaine with levobupivacaine combined with fentanyl for postoperative epidural analgesia in children, failed to show any major benefit of adjunct fentanyl.⁹⁵ Neuraxial administration of opioids still has a place where extensive analgesia is needed, for example after spinal surgery or liver transplantation,^{85,152} or when adequate spread of local anaesthetic blockade cannot be achieved within dosage limits.¹⁸

Neuraxial blockade for paediatric cardiac surgery

The potential benefits and risks of regional anaesthesia for paediatric cardiac surgery have recently been investigated and reviewed.^{21,57,75,76} Single doses of intrathecal opioids with or without local anaesthetic, or continuous spinal anaesthesia using a microcatheter technique appear particularly promising for open heart surgery, while epidural or paravertebral techniques seem to offer benefit for closed procedures. The main concern is that of local bleeding at the site of subarachnoid or epidural puncture in a heparinized child.²¹

Systemic analgesia

The ranking of systemic analgesics in adults by efficacy when administered alone or in combination probably applies also to infants and children.¹¹² However, the pharmacokinetics and pharmacodynamics of these agents change during early life and recent evidence has produced more logical dosing guidelines for opioids, NSAIDs, and acetaminophen (paracetamol) (Tables 2–6).^{8,9,11,15,54,67,70,96,101,114,122,136} Appropriate child-friendly formulations help compliance and are now available as syrups, oral or sublingual wafers, soluble effervescent tablets, and eye drops. Metabolic pathways for many drugs are maturing in early life and indeed

Table 2 Morphine dosing guidelines (an appropriate monitoring protocol should be used)

Titrated loading dose of i.v. morphine
50 $\mu\text{g kg}^{-1}$ increments, repeated up to $\times 4$
I.V. or s.c. morphine infusion
10–40 $\mu\text{g kg}^{-1} \text{h}^{-1}$
PCA with morphine
Bolus dose 20 $\mu\text{g kg}^{-1}$
Lockout interval 5 min
Background infusion 4 $\mu\text{g kg}^{-1} \text{h}^{-1}$ (especially first 24 h)
Nurse controlled analgesia (NCA) with morphine
Bolus dose 20 $\mu\text{g kg}^{-1}$
Lockout interval 30 min
Background infusion 20 $\mu\text{g kg}^{-1} \text{h}^{-1}$

Table 3 Opioids: relative potency and dosing. Appropriate monitoring and ventilatory support must be used

Drug	Potency relative to morphine	Single dose	Continuous infusion
Tramadol	0.1	1–2 mg kg^{-1}	
Morphine	1	0.05–0.2 mg kg^{-1}	10–40 $\mu\text{g kg}^{-1}$
Hydromorphone	5	0.01–0.03 mg kg^{-1}	
Alfentanil	10	5–10 $\mu\text{g kg}^{-1}$	1–4 $\mu\text{g kg}^{-1} \text{min}^{-1}$ or use TCI system
Fentanyl	50–100	0.5–1 $\mu\text{g kg}^{-1}$	0.1–0.2 $\mu\text{g kg}^{-1} \text{min}^{-1}$
Remifentanil	50–100	0.1–1 $\mu\text{g kg}^{-1}$	0.05–4 $\mu\text{g kg}^{-1} \text{min}^{-1}$ or use TCI system
Sufentanil	500–1000	0.025–0.05 $\mu\text{g kg}^{-1}$	Use TCI system

Table 4 Context sensitive half times of opioids in children

Infusion duration (min)	10	100	200	300	600
Remifentanil	3–6	3–6	3–6	3–6	3–6
Alfentanil	10	45	55	58	60
Sufentanil		20	25	35	60
Fentanyl	12	30	100	200	

the proportions of drugs following different routes of metabolism change markedly during this time.^{17 141} For example for morphine or acetaminophen (paracetamol), sulphation is efficient and effective in the early neonatal period with glucuronidation maturing some weeks later. Pharmacogenetics is increasingly recognized as important.⁷⁷ For example, up to 40% of children do not have the enzyme to metabolize codeine to morphine.¹²⁷ Controversy still exists about the safety of NSAIDs for tonsillectomy; whether NSAIDs significantly impede bone healing; and the correct doses of systemic analgesics in less healthy children and in neonates and infants. New agents such as COX-2 inhibitors, new formulations such as i.v. acetaminophen (paracetamol), and properly conducted paediatric pharmacokinetic and pharmacogenetic studies may help solve these problems.

Opioid techniques in children

Morphine infusions of between 10 and 30 $\mu\text{g kg}^{-1} \text{h}^{-1}$ provide adequate analgesia with an acceptable level of side-effects when administered with the appropriate level of monitoring.¹¹⁹ Morphine clearance in term infants greater than 1 month old is comparable with children from 1 to 17 yr old. In neonates aged 1–7 days, the clearance of morphine is one-third that of older infants and elimination half-life approximately 1.7 times longer.^{12 20} In appropriately selected cases, the s.c. route of administration is a useful alternative to the i.v. route.^{111 143} The s.c. route is contraindicated when the child is hypovolaemic or has significant ongoing fluid compartment shifts.¹⁶⁸ Patient-controlled analgesia (PCA) is now widely used in children as young as 5 yr and compares favourably with continuous morphine infusion in the older child.²⁹ A low dose background infusion is useful in the first 24 h of PCA in children, and has been shown to improve sleep pattern without increasing the adverse effects seen with higher background infusions in children and in adults.⁵⁵ Making the hand set part of a squeezable toy is highly popular with younger children. PCA opioid administration is applicable after most major surgical procedures, in sickle cell disease, in management of pain because of mucositis, and in the management of some children with chronic pain. The range of patients receiving opioids in an individually controlled manner can be increased if a nurse or parent is allowed to press the demand button within strictly set guidelines. Monitoring for such patients has to be at least as intensive as that for conventional PCA. Most regimens for nurse or parent controlled analgesia use a higher level of background infusion with a longer lockout time of around 30 min.^{72 97 98 109 117 119} This technology can also be used in neonates where a bolus dose without a background infusion allows the nurse to titrate the child to analgesia or to anticipate painful episodes while allowing a prolonged effect from the slower clearance of morphine (Table 2).

Other methods of opioid delivery

Oral, sublingual, transdermal, intranasal, and rectal routes have been described and have a role in specific cases.^{73 101}

Other opioids

Tramadol, oxycodone, hydromorphone, and buprenorphine may have applicability as alternatives to morphine in the postoperative period.^{59 101 171} Pethidine (meperidine) is not recommended in children because of the adverse effects of its main metabolite, norpethidine. Fentanyl, sufentanil, alfentanil, and remifentanil may have a role after major surgery and in intensive care practice. Remifentanil is very titratable and has a context-insensitive half time with extremely rapid recovery because of esterase clearance, but transition to the postoperative phase is difficult to manage and may be complicated by acute tolerance. It may have a particular role in intraoperative stress control and in neonatal anaesthesia.^{45 46 102 132 138} Sufentanil and fentanyl have long

Table 5 Acetaminophen (paracetamol) dosing guide

Age	Oral		Rectal		Maximum daily dose oral or rectal	Duration at maximum dose
	Loading dose	Maintenance dose	Loading dose	Maintenance dose		
Pre-term 28–32 weeks	20 mg kg ⁻¹	15 mg kg ⁻¹ up to 12 hourly	20 mg kg ⁻¹	15 mg kg ⁻¹ up to 12 hourly	35 mg kg ⁻¹ day ⁻¹	48 h
Pre-term 32–38 weeks	20 mg kg ⁻¹	20 mg kg ⁻¹ up to 8 hourly	30 mg kg ⁻¹	20 mg kg ⁻¹ up to 12 hourly	60 mg kg ⁻¹ day ⁻¹	48 h
0–3 months	20 mg kg ⁻¹	20 mg kg ⁻¹ up to 8 hourly	30 mg kg ⁻¹	20 mg kg ⁻¹ up to 12 hourly	60 mg kg ⁻¹ day	48 h
>3 months	20 mg kg ⁻¹	15 mg kg ⁻¹ up to 4 hourly	40 mg kg ⁻¹	20 mg kg ⁻¹ up to 6 hourly	90 mg kg ⁻¹ day	72 h

Table 6 I.V. acetaminophen (Perfalgan™) (10 mg ml⁻¹) as slow i.v. infusion over 15 min

Weight (kg)	Dose	Maximum daily dose	Dose interval
10–32	15 mg kg ⁻¹	60 mg kg ⁻¹ day ⁻¹ max total 2 g	4–6 h
33–50	15 mg kg ⁻¹	60 mg kg ⁻¹ day ⁻¹ max total 3 g	4–6 h
>50	1 g	Max total 4 g	4–6 h

context sensitive half times but give a smoother transition to maintenance analgesia. Alfentanil has a rapid onset, is titratable, and is relatively context insensitive after 90 min, with a relatively smooth transition in the postoperative phase. The potent opioids may be best delivered by target-controlled infusion devices and paediatric pharmacokinetic programmes have now been developed (Tables 3 and 4).

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are important in the treatment and prevention of mild or moderate pain in children.⁸⁹ NSAIDs are highly effective in combination with a local or regional nerve block, particularly in day-case surgery.^{89,118} NSAIDs are often used in combination with opioids and the ‘opioid sparing’ effect of NSAIDs is 30–40%, as reported for adults.^{10,123} This produces a reduction in opioid-related adverse effects, especially ileus, bladder spasms and skeletal muscle spasms, and facilitates more rapid weaning from opioid infusions or PCA.^{72,74,119,128,159} NSAIDs in combination with acetaminophen (paracetamol) produce better analgesia than either alone.^{10,71,89} Novel formulations of NSAIDs as eye drops have found application after strabismus correction or laser surgery to the eye.¹²² Pharmacokinetic studies of NSAIDs have revealed a higher than expected dose requirement if scaled by body weight from adult doses.^{54,137} NSAIDs should be avoided in infants less than 6 months of age,^{89,115} children with aspirin or NSAID allergy, those with dehydration or hypovolaemia, children with renal or hepatic failure, or those with coagulation disorders, peptic ulcer disease or where there is a significant risk of haemorrhage. Concurrent administration of NSAIDs with anticoagulants, steroids, and nephrotoxic agents is not recommended. The most commonly reported adverse effects of NSAIDs are bleeding, followed by gastrointestinal, skin, central nervous system, pulmonary, hepatic, and renal toxic effects. Other serious side-effects have been reported,

including oedema, bone marrow suppression, and Stevens–Johnson syndrome.^{89,134,136}

NSAIDs and tonsillectomy

Two recent meta-analyses have considered the role of NSAIDs in post-tonsillectomy haemorrhage.^{92,113} One included studies of aspirin, which is not recommended in children.⁹² The other showed a small increased risk of re-operation for bleeding in patients receiving NSAIDs.¹¹³ However, the authors discuss why clear recommendations cannot be drawn from the evidence as the patients receiving NSAIDs benefited from good pain control and reduced PONV.¹¹³ Thus, for every 100 patients, two more will require re-operation if they receive a NSAID than if they do not, but 11 will not have PONV who otherwise would.¹¹³ These meta-analyses did not include studies of COX-2 inhibitors.

NSAIDs and asthma

Provocation of bronchospasm by NSAIDs is thought to be a result of a relative excess of leukotriene production. Aspirin sensitivity is present in about 2% of children with asthma and around 5% of these patients are cross-sensitive to other NSAIDs.⁸⁹ Caution is required in those with severe eczema or multiple allergies and in those with nasal polyps. It is important to check for past exposure to NSAIDs as many asthmatic children take these agents with no adverse effects.¹³⁴ A recent study found no change in lung function in a group of known asthmatic children given a single dose of diclofenac under controlled conditions.¹⁴⁵

NSAIDs and bone healing

Concerns have been raised by animal studies showing impaired bone healing in the presence of NSAIDs.⁸⁹ For most orthopaedic surgery in children, the benefits of short-term perioperative use of NSAIDs outweigh the risks but limitation of use is recommended in fusion operations, limb lengthening procedures, and where bone healing has previously been difficult.⁸⁹

COX-2 inhibitors in paediatrics

Several COX-2 inhibitors have recently been evaluated in paediatrics, although the situation has been complicated by the withdrawal of rofecoxib from worldwide markets.¹⁵⁵ Some early studies used too low a dose,¹³¹ and pharmacokinetic studies are now informing dosing schedules and intervals in children.^{58,146,147} The studies show equal

efficacy to other analgesic interventions with non-selective NSAIDs or acetaminophen (paracetamol) and a morphine-sparing effect, but trials have not been large enough to confirm reduced adverse effects such as bleeding.^{84 144 157}

Acetaminophen (paracetamol)

Acetaminophen inhibits prostaglandin synthesis in the hypothalamus probably via inhibition of cyclooxygenase-3.^{32 142} This central action produces both antipyretic and analgesic effects. Acetaminophen also reduces hyperalgesia mediated by substance P, and reduces nitric oxide generation involved in spinal hyperalgesia induced by substance P or NMDA.

The analgesic potency of acetaminophen is relatively low and its actions are dose-related; a ceiling effect is seen with no further analgesia or antipyresis despite an increase in dose. On its own, it can be used to treat or prevent most mild and some moderate pain. In combination with either NSAIDs or weak opioids, such as codeine, it can be used to treat or prevent most moderate pain.^{10 112} A morphine-sparing effect has been demonstrated with higher doses in day-cases.^{10 90}

Acetaminophen is rapidly absorbed from the small bowel, and oral formulations in syrup, tablet or dispersible forms are widely available and used in paediatric practice. Suppository formulations vary somewhat in their composition and bio-availability, with lipophilic formulations having higher bioavailability. Absorption from the rectum is slow and incomplete, except in neonates.¹⁴ The novel i.v. formulation *pro-paracetamol* is cleaved by plasma esterases to produce half the mass of acetaminophen. Recently, mannitol solubilized paracetamol (PerfalganTM) has become available for i.v. use. Interestingly, the higher effect site concentrations achieved in the brain after i.v. administration may result in higher analgesic potency. Although the site of action of acetaminophen is central, dosing is often based on a putative 'therapeutic plasma concentration' of 10–20 mg ml⁻¹. It is important to realize that the time to peak analgesia even after i.v. administration is between 1 and 2 h. The time-concentration profile of acetaminophen in cerebrospinal fluid lags behind that in plasma, with an equilibration half-time of around 45 min. Very few studies have tried to relate the concentration of acetaminophen in CSF or plasma to measurements of analgesia, particularly in children. There is evidence that a plasma concentration of 11 µg ml⁻¹ or more is associated with lower pain scores. In a computer simulation, a plasma concentration of 25 µg ml⁻¹ was predicted to result in good pain control in up to 60% of children undergoing tonsillectomy.^{8–11 14 15} Dosing regimens for acetaminophen have been revised in the last few years on the basis of age, route of administration, loading dose, maintenance dose, and duration of therapy to ensure a reasonable balance between efficacy and safety. In younger infants, sick children, and the pre-term neonate, considerable downward dose adjustments are needed (Tables 5 and 6).

Conclusions

Moderate and severe postoperative pain can and should be prevented or controlled safely and effectively in all children whatever their age, severity of illness, or surgical procedure. Continuing pain control at home after day-case surgery is essential. The safety of analgesic therapy has improved with the development of new drugs and fuller understanding of their pharmacokinetics and dynamics in neonates, infants and children, and in disease states. These developments have been aided by technical improvements allowing more accurate delivery of analgesia. Where complex analgesia is needed, management by a multidisciplinary acute pain team with paediatric expertise is the most effective approach.

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