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REVIEW ARTICLE

Perioperative management of the child on long-term opioids

Tim Geary[1], Anna Negus[1], Brian J. Anderson[2] & Boris Zernikow[3]

1 Department of Anaesthesia, Starship Children's Hospital, Auckland, New Zealand
2 Department of Anaesthesiology, University of Auckland, Auckland, New Zealand
3 Vodafone Foundation Institute and Chair for Children's Pain Therapy and Paediatric Palliative Care, Children's Hospital Datteln, Witten/Herdecke University, Datteln, Germany

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Correspondence
Prof Brian J. Anderson, Paediatric Intensive Care Unit, Auckland Children's Hospital, Park Road, Auckland, New Zealand
Email briana@adhb.govt.nz

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Summary

The strategies used to manage children exposed to long-term opioids are extrapolated from adult literature. Opioid consumption during the perioperative period is more than three times that observed in patients not taking chronic opioids. A sparing use of opioids in the perioperative period results in both poor pain management and withdrawal phenomena. The child's pre-existing opioid requirement should be maintained, and acute pain associated with operative procedures should be managed with additional analgesia. This usually comprises short-acting opioids, regional or local anesthesia, and adjuvant therapies. Long-acting opioids, transdermal opioid patches, and implantable pumps can be used to maintain the regular opioid requirement. Intravenous infusion, nurse controlled analgesia, patient-controlled analgesia, or oral formulations are invaluable for supplemental requirements postoperatively. Effective management requires more than simply increasing opioid dose during this time. Collaboration of the child, family, and all teams involved is necessary. While chronic pain or palliative care teams and other staff experienced with the care of children suffering chronic pain may have helpful input, many pediatric hospitals do not have chronic pain teams, and many patients receiving long-term opioids are not palliative. Acute pain services are appropriate to deal with those on long-term opioids in the perioperative setting and do so successfully in many centers. Staff caring for such children in the perioperative period should be aware of the challenges these children face and be educated before surgery about strategies for postoperative management and discharge planning.

Introduction

There are few data concerning the perioperative management of the child on long-term opioids. There are no randomized controlled trials examining this topic in adults. There has been a flurry of adult management suggestions in the recent literature (1–10); these are based on case reports, retrospective studies, and expert opinion. Consensus agreement between experts has resulted in management guidelines such as those proposed by the Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine (11) and the American Pain Society (12).

Adults may be opioid dependent as a result of either recreational or therapeutic opioid use including opioid addiction programs. Perioperative pain is often underestimated and under-treated in these patients. Opioid consumption during the perioperative period may be more than three times that observed in patients not taking chronic opioids (13,14) attributable to tolerance, psychopathology, receptor downregulation, altered pain sensitivity, and disease progression. Opioid-induced

hyperalgesia in adults given remifentanil is reported after major abdominal surgery; it is possible that opioid-induced hyperalgesia may occur in those on long-term opioids given additional opioids for postoperative pain (15), but this is not yet reported. A sparing use of opioids in the perioperative period results in both poor pain management and withdrawal phenomena (10). Consensus recommendations include maintaining the patient's pre-existing opioid requirement and managing acute pain associated with operative procedures with additional analgesia. This usually comprises short-acting opioids, regional or local anesthesia, and adjuvant analgesic drugs. Opioids that are slowly metabolized (e.g., methadone), transdermal opioid patches, and implantable pumps are commonly used to maintain the regular opioid requirement. Patient-controlled analgesia (PCA) with higher bolus doses and shorter lock-out intervals have proved invaluable for supplemental requirements postoperatively (14).

The importance of identification of the patient taking long-term opioids, communication between medical teams, collaboration with the patient, staff education, and a strategy for postoperative cares and discharge planning is stressed by most authors (1–10). This current review explores the anesthetic management of children on long-term opioid therapy, suggesting practical approaches to management. Some issues remain contentious, and we have attempted to identify these areas that require further investigation.

Idiosyncrasies of the pediatric population

Analgesic medications and delivery systems commonly used in adults may not be possible or practicable in children. Preschool children are unable to use PCA devices; continuous infusion pumps or nurse-controlled analgesic (NCA) devices are used instead (16). Buccal and sublingual administration in children requires prolonged exposure to the mucosal surface. Younger children find it difficult to comply with instructions to hold drug in their mouth for the requisite retention time (particularly if taste is unfavorable), and this results in more swallowed drug or drug spat out than in adults (17). Bioavailability of an oral transmucosal fentanyl formulation was lower than that in adults, suggesting that many children (3–11 years) swallowed a large fraction of the dose (18). If the drug has a high first-pass effect, then the lower relative bioavailability results in lower plasma concentrations (19,20).

Younger children prefer liquid formulations, and there is a paucity of medicines available in child-friendly formulations or of suitable strengths. Indeed, achieving a single formulation that will have taste acceptance, bioavailability equivalence, and dose accuracy in neonates, infants, children, and adolescents may be excessively costly and even unachievable (21). Although many analgesics are available in an oral liquid formulation, taste is a strong determinant of compliance and unpalatable preparations may be refused (22).

Dosing accuracy can be difficult to achieve when dividing adult tablets for children. Serial dilution of adult intravenous formulations runs the risk of dosing error (23) and also contributes to observed clearance variability (24). Indeed, prescribed doses may be impracticable given an adult preparation (25). When intravenous preparations are given orally, failure to recognize reduced relative bioavailability can result in under-dosing; these 'perfusion-limited' drugs include opioids, propanolol, ketamine, tramadol, and midazolam. In contrast, drugs with 'capacity-limited' clearance (clonidine, diazepam, phenytoin) do not have high first-pass metabolism.

Transdermal therapeutic systems (TTS) designed for adults are sometimes divided and reaffixed in children (26). Dividing and reaffixing patches, which can result in adhesion failure, is not recommended, and the introduction of fentanyl TTS with a drug release rate of 12.5 $\mu g \cdot h^{-1}$ (equivalent to 30 mg morphine per day) has helped match lower dosing requirements of cancer pain control in children (27). Adhesive failure is the most common problem reported to the FDA (28). Adhesion is dependent on factors such as the application site (e.g., movement reduces adhesion), hydration of the skin (oily skin is less adhesive), temperature (sweating), and behavior (picking at the patch) (29). Percutaneous penetration does not alter much with age except in infants; adequate and long-lasting adhesion of a patch is difficult in this age group (30).

In contrast to adult surgery, the majority of pediatric surgical procedures are performed on an outpatient basis (16). If children on chronic opioids are managed in this way, there may be insufficient time for liaison between teams involved in the child's care (e.g., anesthesia, oncology, surgery, psychiatry, chronic pain, and palliative care) and care may be compromised in an effort to reduce time spent in hospital.

Indications for long-term opioid use in children

Recognition of children taking long-term opioids is essential before surgery so that management can be organized. The indication for opioid use will influence subsequent care.

Children are administered long-term opioids for palliative care. 'Long term' for this indication remains

poorly defined, but some have quantified it as beyond 2 weeks of therapy (27,31,32). Opioid use in these children has recently been reviewed (33). While there has been a dramatic increase in adult patients suffering noncancer pain managed with opioids in some countries (12,34), data regarding the use of opioids in children with non-life-limiting conditions are lacking.

The second group is those children and neonates in intensive care units where the duration of opioid receptor occupancy is an important factor in the development of tolerance and dependence (35,36). The qualifying duration of time over which opioids are administered is uncertain and appears agent-, dose-, and time-dependent; up to 20% of children from pediatric intensive care units suffer withdrawal symptoms after opioid cessation (37–39). A third group that should also be considered includes those children recently weaned from chronic opioid use. What constitutes 'recently' is of course open to interpretation and still needs to be clarified in children.

Children requiring repeat surgery (e.g., major burns, staged spinal instrumentation) or children who have frequent disease exacerbations (e.g., sickle cell disease, hemophilia, immune deficiencies, rheumatic conditions) are a fourth group. This group includes those with cancers who are not palliative, but require repeat surgery. These children are commonly receiving opioids for pain.

Illicit opioid use is on the increase among adolescents (40). Adolescents may present with addiction disorder. Their management may be complicated by psychological and behavioral aspects, other drugs of abuse, organ impairment, infectious diseases, and medications used to assist with drug withdrawal and/or rehabilitation (11). Lastly, there exists a very small group of children who are on long-term opioids without a underlying chronic medical disease (41). These children are difficult to manage and might complain preoperatively of severe pain without showing typical pain behavior (described as 'la belle indifference' or an incongruent effect in children with musculoskeletal chronic pain) (42). They request opioids postoperatively partly because they enjoy the psychomimetic effects, particularly relaxation. The indication for surgery (e.g., chronic low back pain) should be questioned in some circumstances (41) where there is no clear indication for chronic opioid use.

Perioperative management

The goals of perioperative management are to provide adequate analgesia, prevent morbidity owing to surgery and anesthesia, and facilitate a return to baseline functioning as quickly as possible while minimizing physical and psychological damage. It is not the goal of the anesthesiologist to wean these children off opioid therapy. Perioperative management is dependent on the nature of the surgical procedure. Few adjustments to routine practice may be required for minor procedures (e.g., lumbar puncture, bone marrow aspiration). These children could receive their oral opioids on the day of surgery and postoperative pain controlled with adjuvant analgesic medications if required. Table 1 outlines important considerations for major surgery.

Preoperative considerations

Assessment and planning are essential. Latham has explored the pre-assessment and management of anesthesia for the pediatric oncology patient (43–45). An outpatient appointment before major surgery may allow the integration of anesthesia, pain, oncology, psychology, and nursing teams along with play therapists and physiotherapists. Perioperative analgesic requirements should be carefully planned, and the family should be aware that opioid requirements will increase postoperatively. Psychosocial factors influence the child's ability to cope and can either improve or worsen the child's suffering, depending on personal and family factors.

Child and parent education

Awareness of the psychological impact of the indication for opioids on both patient and family and the effect of this on pain should not be ignored. An understanding that opioids remain an important part of postoperative pain control and prevention of withdrawal along with the difficulties of transition back to preoperative use is necessary (2). Time should be taken to involve the child and family in decision making and provide education regarding the role of the anesthetist in the perioperative plan (46). Discussion should be made detailing the effects of chronic opioid use on the postoperative period and information presented about the potential for aggravated pain and increased opioid requirements. This includes cessation of PCA devices after recovery from the acute pain insult. If a regional technique is suitable for the patient, time should be taken to adequately inform the patient and family of the reason for this (47).

Play therapy and pain coping strategies such as guided imagery, distraction, and hypnosis may be useful for procedural pain management (48) but are not effective adjuvants for major operations. Behavioral-cognitive strategies may have a role (49,50) after major

Table 1 Considerations for the perioperative management of the child on long-term opioids

Preoperative	Discussion with child and family to include:
	Current opioid use (route, dose, type)
	Potential for increased pain postoperatively
	Explanation for ongoing opioid in perioperative period to prevent withdrawal and necessity for increased opioids use in the short term
	Use of adjuvant therapies
	Method of postoperative analgesia including regional, opioid infusions/PCA
	Planning for transition from oral/TTS systems (if necessary)
	Exploration of patients/family's concerns and anxieties
	Review need for long-term i.v. access
	Discussion with Medical Colleagues:
	Input from acute and chronic pain teams
	Education of primary team including PACU/ward staff regarding perioperative management
	Ensure robust postoperative follow-up mechanisms in place
	Initiation of Perioperative medications:
	Continuation of perioperative opioid/conversion to parenteral opioid
	Preoperative acetaminophen and NSAID unless contraindicated
Intraoperative	Opioid administration and titration to obviate:
	Maintenance requirements
	Intraoperative surgical requirements
	Early postoperative pain
	Implementation of regional anesthesia
	Use of neuraxial/PNB
	Use continuous catheter technique where possible
	Infiltration of local anesthetic or wound catheter
	Commence adjuvant medications
	Acetaminophen and NSAID if not already given/contraindicated
	Ketamine at 2–4 $\mu g \cdot kg^{-1} \cdot min^{-1}$
Postoperative (acute phase)	Titrate analgesic regime/regional anesthetic to patient comfort
	Expect opioid requirements to be 30–100% higher than opioid-naive patients
	Titrate opioids aggressively in PACU to achieve pain control
	Ensure maintenance opioids are continued – if neuraxial technique is used systemic supplementation may be necessary
	Commence opioid infusions/PCA
	Continue regular adjuvant therapies (e.g., tramadol, gabapentin, ketamine, acetaminophen, NSAIDs)
	Consider adding other adjuvants (e.g., clonidine, antidepressants)
	Transition to ward care:
	Appropriate mechanisms in place for monitoring for respiratory depression and over-sedation
	Regular pain assessment, e.g., FLACC, Faces or Paediatric Pain Profile scales
	Input from acute and chronic pain services
Postoperative (transition phase)	Transition from parenteral/regional techniques to oral opioids
	If used for <5 days, they may simply be tapered off over 3–4 days
	Calculate dose requirements over first 24–48 h
	Deliver 50% of the estimated oral dose as long-acting formulation with the remainder as 2–3 hourly breakthrough medication
	Be vigilant for respiratory depression especially with medication with long half-life (e.g., methadone)
	Tapering of oral opioids to preoperative doses
	Reduce over 2–4 weeks unless opioid doses are particularly large
	20–40% reduction in the first 24 h
	Followed by a reduction of 5–10% or 10–20% per day until withdrawal signs are observed
	Treat withdrawal symptoms with opioids not benzodiazepines
	Consider continuing adjuvant medication in the tapering period
	Nonpharmacological techniques can be invaluable (e.g., distraction therapy, TENS)
	Ensure input from Chronic Pain Services in transitioning to long-term management

PACU, post-anesthesia care unit; PNB, peripheral nerve block; TENS, transcutaneous electrical nervous stimulation; TTS, transdermal therapeutic systems; PCA, patient-controlled analgesia; NSAID, nonsteroidal anti-inflammatory drug.

surgery but take considerable time to teach and are not practical for most patients (51). Forward planning is required. The teaching of cognitive therapy, for example, to adolescents with chronic pain and significant functional overload entailed over 110 h (51), and its role is uncertain in the acute postoperative setting. Interventions that focus on the reduction in unhelpful parental behaviors as well as on de-catastrophizing the child's pain problem by teaching parents adaptive coping strategies for the child's pain may prove useful (52). Discharge planning should be considered early so that management of medical conditions, pain, and dysfunction can be continued on return home.

Vascular access

Assessment of the ease of vascular access should be undertaken. If venous access is difficult or if the child is to remain fasted for prolonged periods, central access should be considered as an option for analgesia, nutrition, and fluid balance. When a child already has such access, it is important to review the nonanalgesic medications the child will be receiving in the postoperative period. Multiple infusions that include chemotherapy or inotropes, and drug incompatibilities (53) may warrant the insertion of a second temporary central catheter.

Analgesia

Opioids are known to reduce gastrointestinal activity after both acute and chronic administration (54–56). Preoperative opioid enteral administration may be possible, but reduced gastric emptying times before and during surgery and altered gastrointestinal blood flow may render bioavailability of the opioid difficult to gauge. Basal opioid requirements should be calculated and delivered intravenously on the day of major surgery as an infusion. It may be necessary to convert one opioid to another using equianalgesic daily doses (Table 2). Postoperative ileus may prolong the duration of this requirement. Altered gut function may also affect acetaminophen and nonsteroidal anti-inflammatory drug (NSAID) absorption when administered as premedicants. Intravenous formulations may have better effect.

Although it may seem intuitive to continue TTS application as baseline analgesia, the absorption of TTS drugs is dependent upon consistent peripheral perfusion. Anesthesia may reduce skin perfusion and alter temperature regulation, causing decreased drug absorption. Warming device use during prolonged anesthesia can result in localized increased skin perfusion and increased absorption of drug (1,8,57). Impaired absorption has also been demonstrated in cachectic patients (58). Consequently, for procedures where major alterations in intravascular fluid volume or body temperature are expected or where the surgery is likely to be prolonged, conversion to equianalgesic doses of intravenous opioid is suggested.

Table 2 Estimated daily equianalgesic doses. These dose conversions and others found in the literature (94,114,115) are commonly based on data derived from studies designed to evaluate acute pain relief. There is currently inadequate information for children taking long-term opioids, and this can result in inappropriate dosing (116–118). Further research and studies are urgently needed to improve equianalgesic dosing tables. Clinicians usually titrate the optimal dose during conversion from a reduced calculated dose and base final dose on patient's response

Opioid	Equianalgesic dose
Morphine (the reference opioid)	
Morphine; oral	30 mg
Morphine; i.v.	10 mg
Morphine; s.c.	15 mg
Morphine; rectal	30 mg
Weak opioids	
Tramadol; i.v.	100 mg
Tramadol; p.o.	150 mg
Codeine; p.o.	200 mg
Strong opioids	
Buprenorphine; s.l.	0.3 mg
Buprenorphine; i.v.	0.2 mg
Buprenorphine; transdermal	15 $\mu g \cdot h^{-1}$
Fentanyl; buccal	1 mg
Fentanyl; i.v.	100 μg
Fentanyl; transdermal	12 $\mu g \cdot h^{-1}$
Hydromorphone; i.v.	1.5 mg
Oxycodone; p.o. (immediate release)	15 mg
Hydromorphone; p.o. (immediate release)	4–6 mg
Hydromorphine; i.v.	1.5 mg
Sufentanil; i.v.	10 μg

Consideration should be given to current medication (e.g., methadone) and possible medication interactions (e.g., tricyclic antidepressant and pethidine). Anticonvulsants must not be ceased abruptly as central hyperexcitability might ensue (3). Tramadol may cause seizures or the serotonin syndrome, particularly with overdose or the co-administration of antidepressants (59). Adolescents with addiction disorder should have naltrexone stopped for 24 h (5).

Methadone, despite the stigma associated with its use in patients with addictive disorders, has had a resurgence as an analgesic for chronic pain and palliative care because of its *N*-methyl D-aspartate (NMDA) antagonistic and α-agonistic properties (6). High doses of methadone (>200 $mg \cdot day^{-1}$ in adults) can cause prolongation of the QT interval that may cause ventricular arrhythmias (Torsades de pointes). The risk has been shown to be greatest in those with disease

processes or taking medications (e.g., tricyclic antidepressants) that predispose to a prolonged QT interval. A preoperative electrocardiogram is recommended (6). It is suggested that drugs used in anesthesia known to prolong the QT interval (e.g., ondansetron) be avoided, especially in the presence of reversal drugs at the end of anesthesia during periods of enhanced sympathetic activity (60).

Intraoperative considerations

Opioid requirements

The required opioid dose during surgery comprises the basal requirement and that needed to cover surgical stimulation. Those patients who have been unable to take their maintenance opioid requirements can have this substituted with an equivalent i.v. morphine, fentanyl, or hydromorphone dose at induction (5) (Table 2). For very stimulating procedures, but which traditionally require little postoperative analgesia, short-acting opioids such as alfentanil or remifentanil infusion can be used to augment basal requirements (61).

Individual intraoperative and postoperative opioid requirements can be difficult to determine owing to large between-patient response variability. While total perioperative opioid requirements may be increased threefold, requirements during balanced anesthesia of 30–100% higher than those of opioid-naive patients should be anticipated. Some anesthetists suggest 'front loading' with relatively large doses of opioids at induction, with others favoring half of the estimated dose at induction and titrating the rest during the remainder of the procedure (5). Techniques to determine an individual patient's requirements have been described in adults and include titration of analgesia to clinical observation of respiratory rate and pupil size, and the use of fentanyl infusion to apnea (62,63).

We suggest that the use of spontaneous ventilation during general anesthesia allows a simple and reliable endpoint to gauge the adequacy of opioid therapy. In adults, presence of a respiratory rate >20 with dilated pupils suggests an additional opioid requirement. Titration of further analgesia to a respiratory rate of 12–14 with a slightly miotic pupil generally results in appropriate opioid dosing. This can be extrapolated to pediatric practice by aiming for a respiratory rate slightly lower than normal for age, with a slight miosis. The use of respiratory depression and miosis is impractical in children undergoing major abdominal or thoracic surgery or those positioned in the prone position. Heart rate and blood pressure may serve as crude physiological monitors.

A fentanyl challenge with the endpoint being unresponsiveness or respiratory depression has been described (62,63) in adult opioid consumers for spinal and cardiac surgery. A preoperative infusion of fentanyl was commenced at 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and the total dose was measured once respiratory depression had occurred. Pharmacokinetic modeling was used to estimate a basal infusion and PCA totaling 30% of the dose required to achieve respiratory depression. Few patients subsequently required adjustment to their postoperatively prescribed analgesia regimen. This sophisticated technique has not been used in children.

Opioid analgesic choices

The most commonly used postoperative opioid is morphine, but a child's prior experience of its effectiveness and adverse effects may necessitate consideration of alternatives (3). Morphine is usually continued intravenously (PCA, NCA, infusion) in the immediate postoperative period with a later switch to oral formulations. The calculated daily dose is used as maintenance (e.g., as a background infusion with PCA) and titrated boluses used for breakthrough pain.

Fentanyl may be prescribed for intravenous PCA in the acute phase. Although there is little evidence that using short-acting opioids as rescue medication for breakthrough pain is an optimal long-term treatment strategy in chronic nonmalignant pain, these drugs may have a role immediately postoperatively (64). Intranasal fentanyl spray offers unique advantages over other opioids owing to the ease of administration, high bioavailability (89%), rapid speed of onset (7 min), and a duration of effect of 1 h, making it suitable for rapid control of breakthrough pain, although some children dislike this route (65). Dose in children is uncertain, although doses as low as 20 μg at 5-min intervals have been used for adult cancer-related breakthrough pain (65). Intranasal fentanyl 1.7 $\mu g \cdot kg^{-1}$ has been used in children (7–15 years) for fracture reduction in the emergency department (66). We suggest starting with 0.5 $\mu g \cdot kg^{-1}$ boluses, although higher dose requirements are not uncommon. Buccal and sublingual transmucosal fentanyl citrate has reduced bioavailability but also has potential for breakthrough pain management (33,67–69). Transmucosal oral fentanyl 10–15 $\mu g \cdot kg^{-1}$ has been used to provide analgesia for central venous access removal. Peak concentrations were delayed (53 SD 43 min) in these children (3–11 years), suggesting a large proportion of swallowed drug (18); in contrast, adults given oral transmucosal fentanyl experience rapid analgesic onset (70).

Methadone has a long elimination half-life and protects the patient from acute withdrawal for approximately 1–2 days. Methadone should be continued where possible in the postoperative period; patients will accrue an opioid debt if methadone is stopped, abruptly leading to withdrawal symptoms, hyperalgesia, and difficulty controlling the ensuing pain (6). There are few published pediatric data regarding methadone dosing or conversion ratios with other opioids (33). The conversion rates in adults have ratios of morphine to methadone a 4–5 : 1 (6). Davies *et al.* (71) described conversion ratios in chronic opioid–tolerant children of morphine to methadone between 1 : 2 and 60 : 1, depending on morphine dose (Table 3). Sabatowski *et al.* (72) used conversion rates of 20 : 1 when high morphine doses were used prior to opioid rotation. There remain no uniform guidelines for substituting methadone with another opioid (6).

Buprenorphine is a partial opioid agonist. It is most commonly used as a maintenance alternative to and is better tolerated than methadone in opioid-dependent patients (73). Additional rescue doses of full agonists may then be required with the potential for respiratory depression. Where possible, buprenorphine should be converted to methadone or an alternate long-acting opioid preoperatively (73), although TTS is a possibility (20). Current TTS delivery systems release buprenorphine at 5, 10, 20, 35, 52.5 or 70 $\mu g \cdot h^{-1}$ over a 72-h period. Buprenorphine TTS 35 $\mu g \cdot h^{-1}$ is equivalent to 60–80 $mg \cdot day^{-1}$ of oral morphine (20).

Oxycodone and hydromorphone are alternative choices (33) that are available as immediate and slow-release formulations, intravenously and as suppositories. Oral oxycodone (1.24 $mg \cdot kg^{-1} \cdot day^{-1}$) has been used after pediatric spinal surgery. This is a low dose; the mean ratio of conversion from parenteral morphine equivalents to oxycodone was 1 : 1 (74), and we anticipate a higher dose requirement for opioid-dependent children. The smallest oxycodone dose is 5 mg, making it very applicable to the pediatric population. The oral slow-release formulation provides background analgesia, while the immediate-release formulation is available for breakthrough pain. Oxycodone–naloxone combinations reduce opioid-induced constipation without analgesic loss (75).

The weak opioid codeine, a morphine prodrug, continues to be used (perhaps inappropriately (32)), while tramadol is an alternative for children with moderate pain.

Table 3 Conversion of methadone from morphine is dependent on the total daily dose of morphine

Ratio	Morphine dose (mg)	Methadone dose
4 : 1	30–90	7 mg methadone = 30 mg morphine
8 : 1	90–300	35 mg methadone = 300 mg morphine
12 : 1	>300	35 mg methadone = 400 mg morphine

If the dose of morphine is much higher than 300 mg, then the dose ratio will be higher than 12 : 1 (119,120).

Regional anesthesia

Opioid-tolerant patients should be considered for regional anesthesia because this technique potentially obviates the need for additional opioids (1,4,5,76). It is imperative that if a regional technique is considered as sole postoperative analgesia, arrangements are made to continue oral or parenteral opioids to prevent withdrawal. A theoretical risk of these techniques in chronic opioid users is that with reduction in nociceptive input, the opioid dose is too high and may contribute to respiratory depression.

Neuraxial blockade

The use of neuraxial opioids alone can provide effective postoperative analgesia with fewer adverse effects than systemic opioids in the opioid-naive patient (1). However, as a result of downregulation of spinal opioid receptors, there is a suggestion that intrathecal and epidural dose requirements are increased (13,77,78), but there are no similar pharmacological data in the pediatric population.

The combination of an opioid and local anesthetic is advised for neuraxial blockade because there is no associated change in local anesthetic effectiveness in those with opioid tolerance, although there are reports of reduced duration of blockade (79). The cause of this is uncertain; higher anxiety levels and receptor alterations at multiple levels within the peripheral and central nervous system have been proposed (80). Although patients may experience effective pain relief with a combined opioid/local anesthetic technique, withdrawal may be induced by a failure of the neuraxial opioid to sustain the plasma concentrations necessary to preserve supraspinal receptor occupancy (3) because neuraxial opioid doses are a very small fraction of the basal opioid requirement. Consequently, maintenance of systemic opioid should be continued in the postoperative period. An alternative technique described in adults was to adjust the basal dose of epidural opioid depending on its lipophilic properties, e.g., the dose should be reduced by 80% for morphine but only 20% for fentanyl, and to administer this by epidural with-

out supplementary systemic opioids (3). Lipophilic drugs such as fentanyl and sufentanil are rapidly taken up into blood vessels, the spinal cord, and nerve roots; rostral spread is minimal compared to hydrophilic drugs such as morphine. Monitoring for complications, such as respiratory depression and excessive sedation, when providing opioids via multiple routes of administration, is mandatory (5,81).

Asymmetric cross-tolerance has been described between opioids despite acting at the same receptors. Sufentanil has been recommended as an alternative to intrathecal or epidural morphine when doses are being escalated in the absence of a therapeutic response (82). Equianalgesic doses of central neuraxial morphine and sufentanil have a 60–100 : 1 ratio (82).

The partially effective epidural block can be problematic. Insertion depth and position can be checked with ultrasound although this may be difficult in older children; an epidurogram will confirm the location of the catheter tip in all patients and detect subdural placement as well as placement outside the epidural space (83). A small bolus of local anesthesia (e.g., lidocaine) may help ascertain effect, and the addition of epidural clonidine may rescue a poor epidural. Supplemental analgesia with intravenous opioids may be required, albeit at higher dose than for patients not on chronic opioids.

Peripheral nerve blockade

There are dangers with single-shot peripheral nerve blockade (PNB) because it provides analgesia only for a limited duration. A scenario may occur where a child, who is pain free in the recovery area, later develops uncontrollable pain on the ward while being cared for by those inexperienced in the management of opioid-tolerant patients. Additional plans should be made for delayed postoperative pain. If a patient is undergoing a regional technique, basal opioid requirements must be continued.

Continuous PNB catheter (84) use in pediatric patients have been shown to be as effective as continuous central neuraxial blockade with fewer adverse effects after surgery involving the extremities (85,86). The majority of complications following continuous PNB appear to be motor block and technical issues such as leaking and dislodgement. The use of a tunneled catheter technique may reduce the incidence of the latter.

The post-anesthesia care unit (PACU)

Time should be taken in the immediate postoperative period to assess the effectiveness of the analgesic technique and to check that the appropriate plans are made to safeguard against breakthrough pain and withdrawal. Adequate pain control in the PACU should involve judicious use of adjuvant medications, regional techniques, and appropriate titration of opioids. If a child is undergoing a regional technique, it should be planned to continue at least half of the preoperative opioid requirements systemically; this is thought sufficient to prevent withdrawal in adults (2).

Opioid dose is approximately 1.5-fold the baseline with breakthrough pain covered by either intravenous infusion, NCA, PCA, or oral formulations as required (2,82). Multimodal analgesia should be continued and consideration given to a ketamine infusion if analgesia remains inadequate.

Integration into the care of an acute pain service will provide regular input from staff skilled in managing complex pain issues and highlight problems such as withdrawal or over-sedation. It is important to recognize that a significant proportion of a child's pain may be unresponsive to opioid analgesia and may require alternative pain management strategies, be it adjuvant medication or nonpharmacological methods. It can sometimes be difficult to differentiate chronic pain symptoms from acute postsurgical pain, and members of chronic pain or palliative care services can provide invaluable knowledge and assistance. Communication and education of primary team members and ward staff regarding the specific issues for the patient are imperative and should be commenced prior to surgery.

Management following PACU discharge

The postoperative opioid delivery choice will vary. It may be possible to return to regular slow-release opioids with additional breakthrough medication (either oral or intravenous) after minor surgery. It may be preferable to cease slow-release preparations and convert to equivalent doses of intravenous or epidural opioids after moderate or major surgery (3). Aggressive titration of medication in the early postoperative period is necessary to achieve satisfactory analgesia; there may be reluctance from staff to administer appropriately adequate doses. An infusion of opioid to cover baseline requirements in those unable to take their daily dose of oral opioid should be continued. The demand dose delivered by PCA should equate to the 1-h dose of the background infusion (14).

Postoperative pain management must be guided by regular assessment. This involves regular input from both family and healthcare professionals. Objective scales such as the FLACC scale (Face, Legs, Activity, Cry, Consolability), the Faces Pain Scale, and the

Paediatric Pain Profile remain useful tools for pain assessment (33) in the immediate postoperative period. Complex chronic pain assessment tools do not have a role during this period. An additional focus should be an ongoing assessment to detect potential opioid withdrawal that includes unexplained tachycardia, restlessness, sweating, diarrhea, lacrimation, confusion, and hypertension.

Some children have a reluctance to be weaned from their PCA. It can be sometimes difficult to determine the component from surgical pain and that from underlying chronic pain. For example, children with cerebral palsy undergoing scoliosis correction frequently experience refractory and neuropathic pain (87,88). Management of this aspect should be discussed preoperatively, and transition to oral opioids on an 'as-required' basis progressed early.

Particular consideration should be given to oncology patients who may have an increased incidence of refractory pain and neuropathic pain postoperatively (16,89). This is a result of nerve injury (e.g., stretching or direct trauma) during surgery as well as the effects of adjuvant treatment such as radiation and chemotherapy. These children often have considerable anxiety that contributes to reported pain. Consequently, pain is poorly managed with analgesics alone. An awareness of difficulties in these patients should prompt referral to a specialist pain service and, if necessary, integration of pain management with surgical, oncological care and rehabilitation (16). Adolescents with addiction disorder are also difficult to treat; they may require analgesia for longer periods (14), and concerns of under-medication are countered by anxieties about safety and possible abuse or diversion of the drugs (90–92).

Opioid rotation

Opioid-tolerant patients often experience a reduction in effect of an opioid over time. Opioid rotation has been used as a solution for this reduced effect, intolerance of adverse effects, and intolerance of the mode of delivery (93). For example, constipation is reduced with buprenorphine and transdermal fentanyl (94). Uncontrolled pain with opioids may be better managed with methadone owing to its action on NMDA receptors (95).

Some patients who remain on intravenous long-term opioids may have compromised renal function (e.g., burns, extracorporeal membrane oxygenation), as do some neonates (e.g., gastroschisis with raised intraabdominal pressure). Prolonged morphine infusions result in raised morphine-3 and morphine-6 glucuronide metabolites in children with renal failure. Morphine-3 glucuronide has been suggested to contribute to morphine tolerance (96,97), and rotation to another opioid is a sensible option.

Opioid adjuvants

These drugs diminish opioid requirements (Table 4). Acetaminophen and NSAIDs are usually continued into the postoperative period. These two drugs are opioid sparing when used for acute pain (98) and have an additive effect allowing lower individual doses of each agent (99). Their benefit in patients on long-term opioids is less clear. The opioid sparing effect has minimal impact on opioid adverse effects with large opioid doses, and the adverse effects of NSAIDs after complex surgery (renal dysfunction, platelet function, osteogenesis) are not quantified.

Ketamine, clonidine, and tramadol have a potential place in the immediate postoperative period. Ketamine provides analgesia at low doses (2–4 $\mu g \cdot kg^{-1} \cdot min^{-1}$) largely via NMDA antagonism and has been shown to be effective for chronic pain and neuropathic pain states, particularly neuralgia, dysaesthesia, and allodynia (100,101). In the postoperative period, benefits have been shown through a reduction in opioid requirement, reduced hyperalgesia as a result of opioid excess, and reduced opioid tolerance (2,102).

Tramadol is a weak mu agonist and inhibits reuptake of noradrenaline and serotonin (5HT). It has a wide therapeutic window and exhibits a ceiling effect at doses $> 10\ mg \cdot kg^{-1} \cdot day^{-1}$ (33). Nuclear polymorphism of a functional allele for CYP2D6 causes wide variation in pharmacokinetics between individuals. Tramadol may be administered orally, rectally, intranasally, and intravenously (103).

Table 4 Adjuvant therapies (adapted from reference (33))

Pain type	Adjuvant
Neuropathic pain	Anticonvulsants, antidepressants, corticosteroids, ketamine, regional anesthesia, topical lidocaine
Malignant bone pain	Radiation or radionuclide therapy, corticosteroids, regional anesthesia
Nonmalignant bone pain (e.g., osteoporosis, osteogenesis imperfecta)	Bisphosphonates
Pancreatitis	Ketamine, regional anesthesia
Intracranial pressure, nerve compression	Corticosteroids
Hepatic capsular distension	Corticosteroids
Muscle spasm	Benzodiazepines, baclofen

The α-2-antagonists (clonidine, dexmedetomidine) have a role in the management of opioid withdrawal in adult chronic opioid consumers (2). It has proven useful for the management of neonatal abstinence syndrome (104), although this role has not been fully evaluated in children (33). Opioids and α-2 antagonists have synergistic effects on central sympathetic outflow; α-2 antagonists potentiate the analgesic action of opioids, reducing dose requirement and increasing the duration of action of a single dose of opioid (105).

Gabapentin and pregabalin are useful adjuvants. They are anticonvulsants that work centrally through the calcium channel to reduce the release of glutamate in the dorsal horn of the spinal cord, decreasing neuronal activity. These drugs are rapidly titrated orally, have few adverse effects other than mild sedation and some clouding of mentation, and are largely free of drug interactions. The role of gabapentin given preoperatively to reduce postoperative opioid consumption remains uncertain (1). The target dose for epilepsy is 25–35 $mg \cdot kg^{-1}$ daily for children aged 3–12 years; adult doses of 35–45 $mg \cdot kg^{-1}$ daily titrated to effect can be used in those weighing more than 60 kg (106); the target concentration for pain remains unknown. A dose that is one-third of this is used as a starting dose with rapid escalation over 3 days. However, doses of 40–50 $mg \cdot kg^{-1}$ appear well tolerated in children (106). It is postulated that pregabalin may have fewer adverse effects, and a faster titration schedule may be possible, but this claim has not been substantiated (107,108).

The choice of opioid adjuvant depends on a mixture of anesthetic familiarity, surgical procedure, and underlying pathology. We would suggest the initial use of acetaminophen, NSAIDs, and the addition of ketamine infusion in the immediate postoperative period. Tramadol can be added if required. α-2 Agonists and anticonvulsants (e.g., gabapentin) can be considered later with consultation from other teams. Other adjuvants have specific indications (e.g., tricyclic antidepressants for neuropathic pain (109)).

There is no evidence that benzodiazepines have a specific action in reducing nociceptive pain, but they do have a role in palliation and the treatment for muscle spasms.

Opioid weaning

Perioperative weaning of opioids will depend on the nature of the surgery and its aim in the context of preoperative pain issues. In the majority of cases, once the acute severe phase has been managed, an attempt should be made to reduce opioid requirements toward the preoperative dose. This involves a phase conversion from strong intravenous opioid analgesia to an equianalgesic dose of strong oral opioid analgesia (Table 2). If a regional technique is stopped, an increased opioid requirement may ensue; basal opioid requirements should be met before removing a regional catheter.

The presence of opioid-induced hyperalgesia (110,111) can present a challenge to clinicians. Opioid dose reduction may improve pain in those taking long-term opioids, but this strategy has not been reported in the pediatric acute pain setting (110,112). Ketamine infusion (10–40 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and opioid rotation may be beneficial (15).

Transition phase

A transition phase is required to convert the postoperative analgesic regimen (regional or parenteral) to an oral opioid regime. Patients should continue to be monitored for respiratory depression during periods of transition to long-acting opioids (2,3).

A suggested approach for conversion to oral medication is to calculate the opioid consumed over the first 24- to 48-h postoperative period and then calculate the daily opioid requirement. Half of this daily requirement should be delivered as a long-acting formulation. The remaining opioid can be delivered for breakthrough analgesia every 2–3 h. This approach may not be as valid when regional techniques have been used; increased opioid requirements may become evident as block dissipates and further dose adjustments required.

Once oral analgesia has been established, the next aim is to taper this off to preoperative doses. The postoperative opioid target dose will vary depending on whether the surgical procedure was intended to reduce pain or whether the pain is expected to increase over time. If the postoperative opioid consumption is particularly large, then the transition phase is usually more prolonged (2,3). The tapering regime recommended for children with chronic pain can be implemented; dose is reduced by 20–40% in the first 24 h, followed by a reduction of 5–10% or 10–20% per day until withdrawal signs are observed (33). Withdrawal signs should be treated with more opioid rather than benzodiazepines, and weaning should be temporarily stopped (113). Nonpharmacological approaches (transcutaneous electrical nervous stimulation [TENS], hypnosis, distraction) may prove useful during the transition phase.

Conclusions

Children exposed to long-term opioids require additional considerations during the perioperative period.

Although the strategies used to manage these children are extrapolated from adult literature, most appear applicable to children. Effective management requires more than simply increasing opioid dose to treat acute postoperative pain. Collaboration of the child, family, and all teams involved is necessary. While chronic pain or palliative care teams and other staff experienced with the care of children suffering chronic pain may have helpful input, many pediatric hospitals do not have chronic pain teams and many patients receiving long-term opioids are not palliative. Acute pain services are appropriate to deal with those on long-term opioids in the perioperative setting and do so successfully in many centers. Good communication between all concerned is vital. Staff caring for such children in the perioperative period should be aware of the challenges these children face and be educated before surgery about strategies for postoperative management and discharge planning.

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Conflict of interest

Brian Anderson has received honoraria for consultancies and support for travel costs to conferences from Neuren Pharmaceuticals, Bristol-Myer Squibb, Reckitt Benckiser, SmithKline Beecham and McNiell Pharmaceuticals.

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