Complications of analgesic therapy in children

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Pain frequently accompanies surgical and diagnostic procedures, medical illness, and injury in children and is a leading reason for parents to seek medical attention on behalf of their children. Although many misconceptions contributing to the undertreatment of pain in children have been dispelled over the last 20 years, as pediatric pain management services proliferated, pediatric pain is still not always effectively managed. Complications of analgesic therapy are frequent and may contribute significantly to patient discomfort and family distress, resulting in the decreased use of analgesics and increased pain. Less commonly, adverse effects of analgesic therapy can result in life threatening events such as respiratory depression. Fear of these complications can also result in the undertreatment of pediatric pain. Close surveillance for adverse effects of analgesic therapies coupled with rapid institution of appropriate interventions can reduce the impact of these adverse effects on the quality of patient comfort. The purpose of this review is to provide an overview of adverse effects associated with the analgesic therapies most commonly employed by the pain management service at the Children's Hospital of Philadelphia. Strategies for managing some of these adverse effects will also be discussed.

Tracking clinical activities and outcomes is a desirable feature for any clinical service to facilitate continuous quality improvement. We designed a database to provide our pediatric pain management service with a means to track complications of analgesic therapy as well as a daily census of active patients and monthly and annual activity reports. Between 12/1/2001 – and 12/31/2003, we performed 2693 inpatient consultations (range: 81 -147 consults/month). The average daily census was 16 patients (range: 3 – 35 patients/day). The number of consultations by age groups were: 0-2 months old, 145 consultations; 3-36 months old, 304 consultations; 3-7 years old, 228 consultations; 8-12 years old, 446 consultations; 12+ years old, 1570 consultations. The reasons for pain management consultation included: acute post-operative pain (n=2279), acute non-surgical pain (n=254), chronic pain (n=235), opioid and benzodiazepine dependence (n=34), and anxiolysis (n=-15). The four most common interventions employed were patient-controlled analgesia (PCA) (n=1603), continuous epidural analgesia (CEA) (n=598), continuous intravenous opioid infusion (CIV) (n=270), and patient-controlled epidural analgesia (PCEA) (n=131). Twelve hundred complications were reported in 622 (24%) of the 2602 patients who received one of the four most common analgesic interventions. Four hundred twelve complications were believed to be related to an underlying patient condition and 788 complications (tables 1 & 2) were related to analgesic therapy. The most common complications were: nausea/vomiting (n=239), pruritus (n=223), failed technique (n=50), inadequate analgesia (n=35), sedation (n=31), urinary retention (n=26), epidural catheter dislodged (n=15), headache (n=15), hypoxemia (n=17), hypoventilation (n=9), motor block (n=16), fever (n=17), and hypotension (n=9). Adverse events reported according to patient age and intervention are supplied in table 3 and table 4.

Time and space prevent me from addressing the management of all these adverse effects but I will discuss several. Nausea and vomiting were commonly reported in patients receiving PCA, CIV, CEA, or PCEA. Although some physicians consider these minor problems, many patients and parents view nausea and vomiting as very unpleasant experiences and several reports indicate that nausea and vomiting are leading causes of morbidity in pediatric patients[1]. Even mild nausea and vomiting may result in reduced analgesic consumption, increased pain, delayed return to enteral feeding, delayed hospital discharge, decreased patient and parent satisfaction, and increased reliance on hospital resources including medical and nursing care, intravenous fluids, drugs, and other supplies.

Vomiting is a complicated response mediated by the emetic center located in the medulla. The center receives inputs from many areas of the central nervous system including the chemoreceptor trigger zone, vestibular apparatus, cerebellum, higher cortical and brainstem centers, and the solitary tract nucleus. These structures are rich in dopaminergic, muscarinic, serotonergic, histaminic, and opioid receptors, and blockade of these receptors may be the mechanism of action of antiemetic medications. Pain itself can contribute to emetic symptoms by delaying gastric emptying and also by direct stimulation of the emetic center in the medulla. Kotiniemi et al showed that the incidence of postoperative nausea and vomiting in children increases with the severity of postoperative pain[2]. Systemic and neuraxial opioid therapy of pain can also increase nausea and vomiting by stimulation of the chemoreceptor trigger zone and vestibular apparatus, and by reducing gastric and intestinal motility. Although all opioids are capable of eliciting nausea and/or vomiting, the emetogenic profile of opioids varies considerably from one patient to the next. It is often possible to reduce the severity of opioid-related nausea and vomiting by selecting a different opioid. If nausea and vomiting persists despite the use of an antiemetic agent, we select a different opioid. Also, the use of multimodal analgesia such as combinations of opioids with non-steroidal anti-inflammatory drugs, clonidine, and/or regional anesthesia can result in a reduced incidence and severity of nausea and vomiting [3, 4].

Routine administration of antiemetic agents to all patients receiving PCA, CIV, CEA, or PCEA is not justifiable since the majority of children do not experience nausea and vomiting. Also, commonly used antiemetics can produce disturbing side effects, including sedation, dry mouth, blurred vision, dysphoria, extrapyramidal symptoms, and headache. The serotonin antagonists are relatively devoid of side effects. Consequently, we routinely order ondansetron 0.05 – 0.15 mg/kg IV (maximum 4 mg) every 8 hours PRN nausea or vomiting. Rarely is it necessary to use another antiemetic. Other agents sometimes used include metoclopramide 0.25 mg/kg IV (maximum 10 mg), diphenhydramine 0.5 mg/kg IV, promethazine 0.25 – 1 mg/kg IV, and trimethobenzamide 100 – 200 mg PR. The mixed opioid agonist-antagonist nalbuphine 0.05 – 0.1 mg/kg IV every 4 hours as needed can also be used to treat nausea and vomiting[5]. Nalmefene, a long acting mu antagonist, has also been shown to have antiemetic effects in adult patients on PCA morphine [6]. Prophylactic, low dose naloxone 0.25 - 0.5 mcg/kg/hr has also reduced the incidence of nausea and vomiting without diminishing analgesia [7]. Droperidol, though a great antiemetic, is no longer on our formulary because of the FDA mandated black box warning regarding the potential for life-threatening arrhythmias such as torsade de pointes, especially in individuals with prolonged QT syndrome. Some question the evidence supporting this warning and continue to use droperidol for intractable nausea and vomiting not responsive to other antiemetics [8]. On the other

hand, some authors avoid droperidol because of its dysphoric effects. Scopolamine transdermal patches have also been used to prevent postoperative nausea and vomiting in children on PCA but we avoid scopolamine because of its' potential to cause dysphoria and hallucinations [9].

Pruritus, the second most frequently experienced adverse effect of analgesic therapy in our patients, is also opioid-related. Facial and upper chest itching in the absence of hives are characteristic of opioid-induced pruritus. The itching may be so intense that patients can't rest and they excoriate their skin. The exact mechanism of opioid induced pruritus is unknown. Histamine release does not appear to be causative as opioids which do not cause histamine release can nevertheless produce pruritus and the symptoms are reversed by mu-receptor antagonists such as naloxone[7, 10], nalmefene [6, 11, 12], and nalbuphine [5, 13, 14]. We treat opioid-induced pruritis with nalbuphine 0.05 – 0.1 mg/kg IV every 4 hours as needed. For cases of severe, intractable pruritus usually associated with epidural or intrathecal morphine, we have employed the continuous infusion of naloxone 1-2 mcg/kg/hr. Even lower dose naloxone infusions of 0.25 – 0.5 mcg/kg/hr have been used prophylactically to reduce pruritus [7]. Nalbuphine may be helpful in the antagonism of other mu opioid effects such as nausea, vomiting, urinary retention, and respiratory depression.

The next most common problems reported were failed technique (n=50) and inadequate analgesia (n=35) which fall under the general category of service problems. The vast majority of cases of failed technique were related to epidural analgesia, discovered in the post anesthesia care unit and resulted in abandoning the technique quickly and instituting an alternative pain management strategy. The cases of inadequate analgesia were often detected on rounds the day after surgery and were related to inadequate amounts of analgesic medications or infusion rates and either a lack of communication between the patient's nurse and the resident covering the pain service or a lack of timely or effective response by the resident.

Central nervous system depression (sedation, mental status change, or coma; n=34) and respiratory depression (hypoventilation, hypoxemia, bradypnea, and apnea; n=33) occurred in 0.7% - 1.5% of all patients receiving PCA, CIV, CEA, or PCEA. Surveillance, monitoring, and prompt intervention in all cases prevented a catastrophic outcome. Naloxone 10 mcg/kg IV was administered to 3 patients with respiratory depression and sedation, all less than 18 months of age, and receiving either CEA (n=2) or CIV+CEA (n=1). For children receiving CEA and PCEA, cardiorespiratory monitoring is ordered and oxygen, mask, bag, and suction are made immediately available at the bedside. Respiratory rate is recorded every hour for the first 24 hours after initiation of an epidural infusion (or an increase in the rate of an epidural opioid infusion) and then every 4 hours. Remaining vital signs are recorded every 4 hours. If respiratory rate is less than 12 breathes per minute, oxygen is administered, the pain service is notified, and naloxone 10 mcg/kg SQ is administered if the patient is unarouseable. Continuous oximetry is not required by hospital protocol for patients receiving these interventions but is frequently ordered at the discretion of the pain service.

Urinary retention was reported in 1.2% and 1.9% of patients receiving PCA and CIV, respectively. The vast majority of children with epidural analgesia have foley catheters in place and thus there was only one instance of urinary retention in these patients. In general, if a child is irritable, complains of lower abdominal or perineal pain not related to a surgical incision and has

a palpable bladder, the child's bladder should be catheterized. If the child needs to be catheterized a second time and continued analgesic therapy is required, foley catheter placement should be considered.

The occurrence of fever during the postoperative period is not uncommon. A question that frequently arises is 'when should you remove an epidural catheter in a febrile patient?' The theoretical risk of seeding the epidural space with bacteria and developing an epidural abscess is the major concern in this situation. Aside from a few case reports, there is little literature to guide our practice here. Epidural abscesses have been reported in 2 immunocompromised children who continued to receive epidural infusions for terminal cancer pain management despite repeated febrile episodes[15, 16]. Cutaneous and subcutaneous abscesses developed in 2 infants while they were receiving continuous epidural infusions for pain management following Kasai procedures for biliary atresia[17]. These infants had been febrile and developed ascending cholangitis. In making the decision to remove an epidural catheter because of fever, one must consider the fact that epidural abscess formation is a catastrophic complication and an alternative analgesic therapy can usually be instituted which results in satisfactory pain management. In any febrile child receiving continuous epidural analgesia, a thorough evaluation for signs of a superficial or epidural abscess formation is required including the presence of localized inflammation at the epidural insertion site (redness, swelling, discharge), back pain, radicular pain, or sensory or motor deficits not explained by the epidural infusion. If any of these are present, the epidural catheter should be removed. Neuroimaging studies and neurosurgical consultation should be obtained urgently if an epidural abscess is suspected. In the absence of the above signs, we consider removing an epidural catheter in a child with a sustained temperature elevation over 38.5^{o} C for more than 12 hours or in children with repeated febrile episodes over 39^{o} C. If the child is immunocompromised, if the bio-occlusive epidural dressing has become detached, if the epidural catheter has been contaminated with fecal material, or if the epidural catheter has been in place for over 48 hours, we would consider removing the catheter.at a shorter interval after fever develops.

The purpose of this presentation has been to provide an overview of the adverse events reported over the last 25 months in patients on the pain management service at the Children's Hospital of Philadelphia. Prompt recognition and treatment of adverse events can result in improved patient comfort and safety.

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Table 1: Adverse events related to PCA, CIV, CEA, & PCEA.

System	Adverse Event	N
General/Skin	**All**	**252**
	Pruritus	223
	Fever	17
	Epidural site inflammation	5
	Hives/rash	4
	Fecal Contamination Caudal Cath	3
Gastrointestinal	**All**	**250**
	Nausea/vomiting	239
	Constipation	7
	Abdominal pain	2
	Ileus	2
Neuro/Psych	**All**	**98**
	Sedation	31
	Motor Block	16
	Headache	15
	Dizziness	8
	Paresthesia/Dysesthesia	7
	Myoclonus	6
	Irritability	4
	Nightmares/Hallucinations	3
	Dysphoria	3
	Horner's Syndrome	2
	Coma	2
	Mental Status change	1
Respiratory	**All**	**33**
	Hypoxemia	17
	Hypoventilation	9
	Bradypnea	4
	Apnea	3
GU	**Urinary Retention**	**26**
Cardiovascular	**All**	**11**
	Hypotension	9
	Arrhythmia	2
Total		**670**

Table 2: Other reported Complications in patients receiving PCA, CIV, CEA, and PCEA.

Service problems	**All**	**118**
	Failed technique	50
	Inadequate Analgesia	35
	Epidural Catheter dislodged	15
	Pump Malfunction	9
	Medication Errors	9

Table 3: All adverse events by age & intervention (Adverse events/patients).

	0-2 mo	**3-36 mo**	**3-7 yr**	**8-12 yr**	**12+ yr**	**TOTAL**
CIV	2/21	16/89	20/80	7/36	11/44	56/270
PCA	0/0	0/32	14/47	64/311	351/1213	429/1603
CEA	18/131	44/172	51/88	40/75	64/132	217/598
PCEA	0/0	2/3	0/1	4/13	80/114	86/131
TOTAL	20/152	62/296	85/216	115/435	506/1503	788/2602

Table 4: The number (%) of most commonly reported adverse events (n ≥ 17) by intervention.

	PCA , n=1603	**CIV, n=270**	**CEA, n=598**	**PCEA, n=131**
Nausea/vomiting	183 (11.4%)	14 (5.2%)	23 (3.8%)	18 (13.7%)
Pruritus	132 (8.2%)	15 (5.6%)	46 (7.7%)	30 (22.9%)
Failed Technique	3 (0.2%)	0 (0%)	39 (6.5%)	8 (6.1%)
Inadequate Analgesia	10 (0.6%)	5 (1.9%)	17 (2.8%)	3 (2.3%)
CNS Depression	22 (1.4%)	2 (0.7%)	8 (1.3%)	2 (1.5%)
Respiratory Depression	21 (1.3%)	4 (1.5%)	7 (1.2%)	1 (0.8%)
Urinary Retention	20 (1.2%)	5 (1.9%)	1 (0.2%)	0 (0%)
Fever	2 (0.1%)	0 (0%)	11 (1.8%)	4 (3.1%)