Use of Buprenorphine in Children With Chronic Pseudoobstruction Syndrome

Case Series and Review of Literature

Sunisa Prapaitrakool, MD, Markus W. Hollmann, MD, PhD, DEAA, Hans Christian Wartenberg, MD, Benedikt Preckel, MD, PhD, MA, DEAA, and Stefan Brugger, MD

Objectives: Abdominal pain is the most challenging symptom in chronic intestinal pseudoobstruction (CIPO) syndrome, because of its severity and the limited availability of suitable opioid formulations, especially in pediatric patients with digestive problems. Most of the children with CIPO cannot tolerate oral formulations.

Case Reports: We present 4 cases of children with CIPO and severe intractable abdominal pain, and report on the use of a recently available form of opioid, transdermal buprenorphine in a dosage of 5 mcg/h.

Discussion: CIPO and the unique pharmacological profile of buprenorphine are reviewed briefly.

Key Words: pediatric, pain management, transdermal buprenorphine


Chronic intestinal pseudoobstruction (CIPO) was first described in 1958. It depicts a rare disorder in which impaired intestinal motility results in symptoms of bowel obstruction in the absence of mechanical causes. Etiology can be primary or secondary to an underlying disorder affecting neuromuscular function. Most pediatric cases are of congenital origin, associated with a poor long-term outcome. The mortality rate of children with CIPO ranges from 10% to 25%, partly due to other comorbidities, for example, urinary tract involvement, bowel malrotation, and immunodeficiency.

Clinical manifestations depend on the affected area of the gastrointestinal tract and may include nausea, vomiting, abdominal distension, abdominal pain, constipation, malnutrition, and/or other symptoms, such as periods of diarrhea after bacterial overgrowth. However, morbidity and mortality are mostly related to the long-term use of total parenteral nutrition (TPN). Although there is limited evidence for clinical therapy in these children, management of CIPO patients should include a multidisciplinary approach involving gastroenterological medication, antibiotics, nutritional support, surgical options, and pain management, and psychological support. CIPO children and their families receive this support in our institution.

Lindberg et al. demonstrated that abdominal pain was the most common symptom in CIPO with respect to adults. Although pain is not considered one of the 3 main symptoms of CIPO in children, for those with pain, a pain specialist should be involved, as it can be extremely difficult to treat. Many of these children need strong analgesics to control their pain, and overdoses can become detrimental. Severe intractable pain causes disease-related poor quality of life for the patient and their families.

Despite a variety of opioid preparations currently on the market, digestive problems in CIPO limit potential routes of administration. Although opioids are known for their at times severe side effects on gastrointestinal motor activity, because of the severity of the pain, opioids are very often unavoidable. Transdermal opioid applications may cause less constipation, but this has not been reported for buprenorphine usage in children. Transdermal opioid application seems to be the preferable formulation for these children because of its capacity to maintain a constant plasma level for days without the necessity of oral intake. Since the recent launch of low-dose transdermal buprenorphine (BuTrans), reports of proven efficacy, tolerability, and a safety profile for chronic cancer and noncancer pain in adults were published. However, little experience exists regarding the use of low-dose BuTrans in children, with only 1 report in children with cancer pain and very little pharmacological data concerning buprenorphine in children.

We describe our experience with BuTrans as the primary analgesic medication in 4 children with CIPO to achieve favorable pain control for these patients. We have chosen buprenorphine, because it is available as a transdermal formulation, and it has a high receptor affinity combined with a high potency and a low risk for euphorogenic effects.

CASE REPORTS

We reviewed all pediatric pain consults at the Academic Medical Center Amsterdam since 2007 and identified 4 cases of CIPO with severe intractable pain (Table 1). All children were boys, aged 3 to 10 years at first consultation, with symptoms mostly present since birth. All cases were diagnosed with CIPO by specialists in pediatric medicine. This diagnosis is mainly clinical, supported by radiography of a dilated bowel with air-fluid level and exclusion of other organic causes, as detected by radiologic and/or endoscopic examination. The children received initial pain treatment by pediatric gastroenterologists before the chronic pain consults.
Case 1
A 4-year-old boy with progressive digestive problems since his birth and who was later diagnosed with CIPO. Medication included omeprazole, vancomycin, paracetamol, and diclofenac. Progressive abdominal pain persisted after adding tramadol. His parents described the pain as cramping, aggravating at night, and sleep disturbing.

We increased tramadol up to 10 mg every 6 hours, but oral intake aggravated his abdominal pain. Eventually, TPN became necessary. tramadol 15 mg was administered with the TPN 4 times a day; however, the pain became worse as the disease progressed.

Analgesic therapy was changed to low-dose BuTrans to control background pain, and fentanyl nasal spray was used for breakthrough pain. Despite the absence of a patch application for the sublingual formulation of buprenorphine nor the oromucosal formulation of fentanyl was tolerated, as the patient believed that everything taken orally causes pain. BuTrans was started at a dose of 5 mcg/h and replaced every 7 days. Fentanyl nasal spray, which was specially dispensed by the local pharmacist, was given at 25 mcg per dose when needed up to 4 times a day. Using this regimen significant pain relief was achieved within days, and tramadol could be stopped. After 2 further consultations within the next month, satisfactory pain control was achieved at a BuTrans dose of 10 mcg/h, with fentanyl nasal spray for breakthrough pain. This analgesic regimen remained sufficient and unchanged for 1 year. Merely a skin reaction to the patch including erythema and pruritus at the affected area was observed. Using topical steroid spray before patch application and after patch removal, and reducing patch replacement time to 4 days, prevented further adverse skin reactions.

Case 2
A 3-year-old boy presented with severe abdominal pain and was diagnosed with CIPO. Comorbidities included asthma and multiple food allergies. Digestive symptoms were difficult to control and required frequent hospitalization, sometimes for months. The boy underwent gastrostomy, and later jejunostomy along with TPN for feeding. Pain was accompanied by nausea and vomiting and was more severe at night, which made him wake up every hour, cry vigorously, scream, and pull his hair. Medication included ventolin inhaler, esomeprazole, erythromycin, hyoscine butylbromide, paracetamol, and a laxative. Initially, tramadol drops were administered through gastrostomy, but pain relief could not be achieved despite dose adjustment up to 15 mg every 4 hours. Analgesic therapy was then substituted with BuTrans 10 mcg/h patch, replaced every 7 days to control background pain, and sublingual buprenorphine (Temgesic) 0.05 mg for breakthrough pain. Sublingual application was managed by the parents. Sufficient pain control was achieved after a few days. A topical steroid spray was used at the site of buprenorphine patch application to prevent local skin reaction. Parents were satisfied with their son’s sleep. No adverse reaction resulted from the analgesic regimen, which has been satisfactorily continued up to now for 7 months.

Case 3
A 10-year-old boy was referred to the pain clinic with severe abdominal pain and several medical problems. He was suffering from CIPO since the age of 3 years and had been on TPN for several years. His comorbidities included severe immune deficiency with unsuccessful bone marrow transplantation. Varicella Zoster viral infection at the age of 4 was complicated by pneumonia, hepatitis, liver cirrhosis, and portal hypertension. One year ago, he suffered from upper gastrointestinal bleeding, which was managed by medical treatment and blood transfusion. In addition, osteoporosis with compression of the thoracic and the lumbar spine from T9 to L3 with no surgical options was present. Physical examination revealed marked jaundice and hepatosplenomegaly due to advanced liver disease, which placed him on the transplant list.

Psychologically, the patient was very emotional and easily angered. He described his pain as a dull persistent pain in the right upper abdominal quadrant with a numeric rating scale intensity of 7/10. His medication consisted of paracetamol, tramadol, codeine, metoclopramide, and a laxative. He also used low-dose BuTrans and sublingual fentanyl at 0.1 mcg/h and fentanyl nasal spray 50 mcg per dose every 4 hours if necessary. Still, the patient did not consistently achieve adequate pain relief, and 5 mg of oral morphine, no more than 3 times a day, was added to the regimen. His general condition deteriorated due to severe liver cirrhosis and occasionally required hospitalization. Pain was under control with 25 mcg/h transdermal fentanyl and fentanyl nasal spray 50 mcg 4 times a day.

The boy unexpectedly reported a short period of nausea after the exchange of the 2 fentanyl patches, which significantly improved with a 6-hour delay between the patch exchanges. Up to now, this pain therapy has been successfully continued.

Case 4
A 9-year-old boy with a long history of CIPO presented with early symptoms at the age of 3 years. His feeding was mainly achieved through jejunostomy. Referral to our pain clinic was initiated because of a severe burning, aching sensation localized at the jejunostomy. Analgesic medication at the first consult consisted of paracetamol, diclofenac, and fentanyl nasal spray. BuTrans 5 mcg/h and sublingual buprenorphine were added. Favorable pain relief was achieved after the first application of the buprenorphine patch, and oral pain medication could be stopped. The patient preferred sublingual buprenorphine for breakthrough pain instead of fentanyl nasal spray. However, as he reported sufficient pain relief with transdermal buprenorphine, he rarely needed the sublingual formulation. BuTrans was generally well tolerated, with only mild pruritus of the skin at the application area, which disappeared after patch removal.

**DISCUSSION**

Buprenorphine is a semisynthetic long-acting opioid with a potency of 25 to 40 times that of morphine. It is a partial agonist at the μ-opioid receptor and an antagonist at

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (y)</th>
<th>Male/Female</th>
<th>Buprenorphine Dose (mcg/h)</th>
<th>PRN Pain Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>4</td>
<td>Male</td>
<td>10</td>
<td>Fentanyl nasal spray (25 mcg up to 4/d)</td>
</tr>
<tr>
<td>Case 2</td>
<td>3</td>
<td>Male</td>
<td>10</td>
<td>Sublingual buprenorphine (50 mcg)</td>
</tr>
<tr>
<td>Case 3</td>
<td>10</td>
<td>Male</td>
<td>15</td>
<td>Sublingual buprenorphine (50 mcg up to 6/d)</td>
</tr>
<tr>
<td>Case 4</td>
<td>9</td>
<td>Male</td>
<td>5</td>
<td>Sublingual buprenorphine (50 mcg rarely)</td>
</tr>
</tbody>
</table>

PRN indicates Pro re nata.
the k-opioid and the δ-opioid receptors. Studies in rats and humans confirmed less respiratory depression with a ceiling effect for buprenorphine compared with other potent opioids. Its water solubility, lipophilicity, and low molecular weight contribute to its capacity to be delivered by transdermal formulation, available since 2001 at dosages of 35, 52.5, and 70 mcg/h over a period of 96 hours. Recently, transdermal formulations have been available at 5, 10, and 20 mcg/h over a period of 7 days, allowing small-dose titration. BuTrans is well tolerated, with the most common systemic side effects being nausea (9.2%) and dizziness (4.6%), whereas the most common local side effects are erythema (12.1%) and pruritus (10.5%).

Abdominal pain caused by CIPO is primarily visceral pain due to mechanical stretching, distension, contraction, or torsion, thereby stimulating visceral nociceptors. Because of the bilateral symmetric innervation of the digestive system, pain from this origin is felt in the midline, usually ill defined and poorly localized or reported periumbilically. Two of the presented cases illustrate this typical visceral pain. In 1 patient (case 3), pain was complicated by hepatosplenomegaly, resulting in upper abdominal pain and discomfort mainly during daytime. In case 4, previous surgery might have caused somatic/neuropathic pain. Pain in the latter 2 patients thus may have resulted from CIPO, comorbidities, or previous surgery.

Analgesics used in patients with CIPO include non-opioid (paracetamol, nonsteroidal anti-inflammatory drugs) and opioid drugs. Antidepressant and anticonvulsant drugs, which are widely used in adults, are considered unsafe for children. Data on antidepressant use in children less than 18 years old showed an increased risk of hostility, mood swings, aggression, and suicide. Consequently, a recent Cochrane review did not recommend its use. More recent studies showed that adolescents with chronic irritable bowel syndrome benefit from an antidepressant therapy, whereas children had no clear benefit. Anticonvulsant drugs are mainly used in neuropathic pain and might therefore not be effective for abdominal pain in CIPO. In addition, behavioral changes including tantrums, aggression, and hyperactivity after use of gabapentin in children have been reported. Therefore, the side-effect profile limits the use in children. In our cases, paracetamol and nonsteroidal anti-inflammatory drugs were used as adjuvants, but, given the severity of the pain, analgesic therapy mainly relied on opioids. If pain is poorly controlled by morphine or side effects are dominant, BuTrans might be an option.

Nonoral formulations play an important role as analgesics in children. Although the smallest available fentanyl patch is 12 mcg/h, the smallest transderapeutic system for buprenorphine is 5 mcg/h, allowing easier dose adjustment in pediatric cases. Three of 4 children with CIPO achieved satisfactory pain control with buprenorphine; in contrast, fentanyl achieved more favorable pain relief in 1 case supporting an individual response to different opioids. Side effects such as nausea and vomiting occurred in 1 of 4 cases and unfortunately precluded further use of the opioid at a higher dose. However, this boy experienced nausea and vomiting also with other opioids. He chose to continue with fentanyl, which gave him better pain relief with less nausea and vomiting compared with buprenorphine.

The most common problems in our pediatric cases were local skin reactions (in 3 of 4 patients) ranging from mild pruritus to erythema, which responded well to topical steroid spray. General recommendation to avoid skin reaction is to change the patch site at every new replacement, avoiding the previous site for up to 4 weeks. In 1 case, we had to reduce the application time of BuTrans to 4 days, instead of 7 days as usual.

During 1 to 3 years’ follow-up, the dose requirement of buprenorphine remained constant for a long period after achieving pain relief, suggesting less opioid tolerance, probably due to the dominant spinal working mechanism of buprenorphine, which has less effects on the brain and causes lower risk of drug abuse and addiction.

In summary, effective pain management is one of the key supportive treatments in children with CIPO, and BuTrans could be a safe and effective alternative in many cases. In our case series, opioid rotation and dose adjustment could be managed safely on an outpatient basis. Small-dose patches of buprenorphine allow titration of the drug even in younger children. Adverse effects seen in terms of skin reaction can be managed easily. Further clinical studies are needed to confirm these findings.

REFERENCES


