The Effects of a Small-Dose Naloxone Infusion on Opioid-Induced Side Effects and Analgesia in Children and Adolescents Treated with Intravenous Patient-Controlled Analgesia: A Double-Blind, Prospective, Randomized, Controlled Study

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Opioids are frequently associated with side effects such as nausea, vomiting, and pruritus. We hypothesized that a prophylactic, continuous small-dose naloxone infusion would reduce the incidence of opioid-induced side effects without affecting analgesia or opioid consumption. In this prospective, double-blind, randomized, controlled clinical trial, we studied 46 postoperative patients (M:F, 21:25), averaging 14 ± 2.5 yr and 53 ± 17 kg, at the start of morphine IV patient-controlled analgesia. Patients were randomized to either saline (control, $n = 26$) or naloxone 0.25 $\mu g \cdot kg^{-1} \cdot h^{-1}$ ($n = 20$). We found that the incidence and severity of pruritus (77% versus 20%; $P < 0.05$) and nausea (70% versus 35%; $P < 0.05$) was significantly more frequent in the placebo group compared with the naloxone group. Morphine consumption (1.02 ± 0.41 $mg \cdot kg^{-1} \cdot d^{-1}$ versus 1.28 ± 0.61 $mg \cdot kg^{-1} \cdot d^{-1}$), pain scores at rest (4 ± 2 versus 3 ± 2), and pain scores with coughing (6 ± 2 versus 6 ± 2) were not different. We conclude that, in children and adolescents, a small-dose naloxone infusion (0.25 $\mu g \cdot kg^{-1} \cdot h^{-1}$) can significantly reduce the incidence and severity of opioid-induced side effects without affecting opioid-induced analgesia. When initiating morphine IV patient-controlled analgesia for the treatment of moderate to severe pain, clinicians should strongly consider starting a concomitant small-dose naloxone infusion.

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In patients of all ages, opioids are the cornerstone of management of moderate to severe pain (1,2). Regardless of the method of administration, all opioids produce unwanted side effects, such as pruritus, nausea and vomiting, constipation, urinary retention, cognitive impairment, tolerance, and dependence (3). Indeed, many patients suffer needlessly because they would rather experience pain than these opioid-induced side effects. Additionally, physicians are often reluctant to prescribe opioids because of these side effects and because of their fear of other less common, but more serious, side effects such as respiratory depression.

Naloxone, an opioid receptor antagonist, is effective at reducing and antagonizing both desired and undesired opioid effects. Several clinical and laboratory studies have demonstrated that small-dose naloxone infusions can treat or prevent opioid-induced side effects without affecting the quality of analgesia or opioid requirements (4–6). Based on these previous studies, we hypothesized that a small-dose naloxone infusion (0.25 $\mu g \cdot kg^{-1} \cdot h^{-1}$), when administered

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prophylactically, could prevent the most common undesired side effects of opioid administration (pruritus, nausea, and vomiting) in children and adolescents receiving morphine IV patient-controlled analgesia (PCA) for moderate to severe postoperative pain.

Methods

After obtaining IRB approval, parental informed consent, and, when applicable, patient assent, male and female ASA physical status I–III patients, older than 6 and younger than 18 yr of age, with acute, moderate to severe, postoperative pain were studied. Surgical procedures included major orthopedic (spinal fusion and lower extremity osteotomies), neurosurgical (cervical decompression), or pectus excavatum surgery. Patients were recruited by a study investigator before surgery, and the study protocol was instituted in the immediate postoperative period. Exclusion criteria included patients who remained tracheally intubated after surgery, who required concomitant benzodiazepine administration, who were unable to initiate a bolus (demand) dose (mental or physical disability), and who were unable to communicate verbally. Additionally, patients who were allergic to opioids, were in any investigational drug trial within 1 mo of the treatment day of the study or who received opioids within 7 days of the study were excluded.

We planned to study 64 male and female inpatients divided into two groups (32 in each group). Based on previous investigations in adults (4) and on an analysis of our Pediatric Pain Service database, the incidence of nausea, vomiting, and pruritus in patients treated with morphine IVPCA ranges between 50% and 60% for nausea and vomiting and less than 60% for pruritus. The number of patients required to identify a 50% difference in the incidence from 60% to 30% with an $\alpha = 0.05$ and $\beta = 0.2$ is 64. Data were stored on Excel 2000 (Microsoft Corporation, Redmond, WA) and analyzed with STATA® statistical software, version 6.0 (StataCorp, LP, College Station, TX). Descriptive statistics and χ^2 analysis were used where appropriate to analyze data. Data are presented as mean ± SD, and P values <0.05 were considered statistically significant.

Although intraoperative general anesthetic management was not standardized, all patients enrolled in this study underwent general anesthesia, during which they were routinely monitored, paralyzed with nondepolarizing muscle relaxants, and endotracheally intubated. After antagonism of neuromuscular blockade with neostigmine and atropine, patients were tracheally extubated and transported to either the pediatric postanesthesia care unit (PACU) or the pediatric intensive care unit (PICU) for recovery. On arrival to the PACU or PICU, patients were started on IVPCA (CADD Prizm, Sims Deltec, St. Paul, MN). The PCA pump cassette contained 100 mg of morphine sulfate in 100 mL of normal saline (1 mg/mL). The following routine settings were established: an initial dose of up to 100 μg/kg or more to achieve patient comfort, a maintenance basal infusion rate of 20 $\mu g \cdot kg^{-1} \cdot h^{-1}$, a demand dose of 20 μg/kg, a lockout time interval of 8 min, and a maximum of five doses per hour (7).

Patients were randomly assigned by the hospital's investigational drug pharmacy to one of two groups using computer-generated random numbers. Group 1, the study group, received 0.25 $\mu g \cdot kg^{-1} \cdot h^{-1}$ of naloxone by continuous infusion. The naloxone was administered by a continuous infusion pump "piggybacked" into the patient's IV catheter. The naloxone solution was prepared in the pharmacy by mixing 2 mg of naloxone in 250 mL of 0.9% saline (final concentration = 8 μg/mL). Group 2, the placebo group, received only saline by the infusion pump. The study solutions were prepared by the pharmacist and diluted in saline to produce equal volumes to ensure proper blinding. The study was double-blind, with the patient, patient's family, anesthesiologist, pediatric pain service, nursing staff, and observers all unaware of the randomization.

Every 4 h while awake, patients were evaluated for pain and for the incidence of side effects by either their nurse or by a study nurse. We evaluated subjective pain scores and the 24-h cumulative incidence and frequency of vomiting, nausea, pruritus, and respiratory depression over the observation time periods. Subjective pain scores were assessed at rest and with activity (coughing and deep inspiration). We used two types of subjective pain scores; in younger children, we used the Wong Baker Faces scale (a cartoon containing six faces), and in older children, we used a 0–10 scale (8). Additionally, patients were asked to self-assess pruritus and nausea (0 = none, 1 = present but tolerable, and 2 = severe, intolerable) and were asked if they had vomited. The 24-h nursing bedside flow sheets were scrutinized for episodes of nausea and vomiting. Vital signs, including arterial blood pressure, respiratory rate, and oxyhemoglobin saturation were monitored and recorded every 4 h.

Patients who developed opioid-induced side effects while on the study protocol were treated symptomatically. Nausea and vomiting was treated with IV ondansetron 0.1 mg/kg (maximum dose 4 mg); pruritus was treated with IV diphenhydramine 1 mg/kg (maximum dose 50 mg). If these drugs did not relieve the symptoms, the opioid contained within the PCA cassette was changed from morphine (1 mg/mL) to an equianalgesic dose of hydromorphone (0.2 mg/mL) (9). If these maneuvers did not relieve the symptoms, the study was terminated, and the patient was treated with a continuous IV naloxone infusion at 1 $\mu g \cdot kg^{-1} \cdot h^{-1}$. If respiratory depression occurred (respiratory rate <8 breaths/

Table 1. Patient Demographics

	Placebo $n = 26$	Naloxone $n = 20$
Age (yrs)	13.7 ± 2.3	13.7 ± 2.7
Weight (kg)	53.6 ± 17	52.9 ± 17.4
Sex (M:F)	11:15	10:10
Duration of IV PCA therapy (days)	2 ± 1	2 ± 1
Posterior spinal fusion	15	9
Pectus excavatum repair	6	4
Lower extremity osteotomies	2	2
Chiari malformation	1	3
Other	2	2

PCA = patient-controlled analgesia.

min, Sao_2 <90%, and the patient was unarousable), the IVPCA was turned off, and the patient was given naloxone 1 μg/kg IV emergently. If this dose was ineffective, the dose was doubled every minute until the patient awakened and had adequate respiratory effort. Finally, the amount of morphine used and the requirements for supplemental analgesia or symptomatic treatment over 24 h were also recorded.

Results

Forty-six patients (M:F, 21:25), averaging ±SD 14 ± 2.5 yr (range, 6–17 yr) and 53 ± 17 kg (range, 14–101 kg), were studied. There were no differences in the demographic data between the groups (Table 1). An unplanned interim analysis of the data from these 46 patients was performed because the patient accrual rate was slower than expected and because two of the principal investigators (LGM and SCK) left the institution. This interim analysis resulted in early closure of the study because there were significant differences in the outcomes between the two treatment groups.

Three patients were withdrawn from the study because of the severity of their opioid-induced side effects and because of our inability to treat their opioid-induced symptoms with rescue medications. All three were in the placebo group. The incidence and severity of pruritus was nearly four times more in the placebo group when compared with the naloxone group (77% versus 20%; $P < 0.05$) (Fig. 1). The incidence and severity of nausea among children in the placebo group was twice that of the naloxone group (70% versus 35%; $P < 0.05$) (Fig. 1). Five children in the treatment group vomited compared with 12 in the placebo group (25% versus 46%; NS). Naloxone-treated patients seemed to have fewer requests for rescue antiemetic and antipruritic medication compared with the placebo group. However, the difference was not significant. Four patients in the placebo group and one patient in the naloxone group required a change in opioid from morphine to hydromorphone to

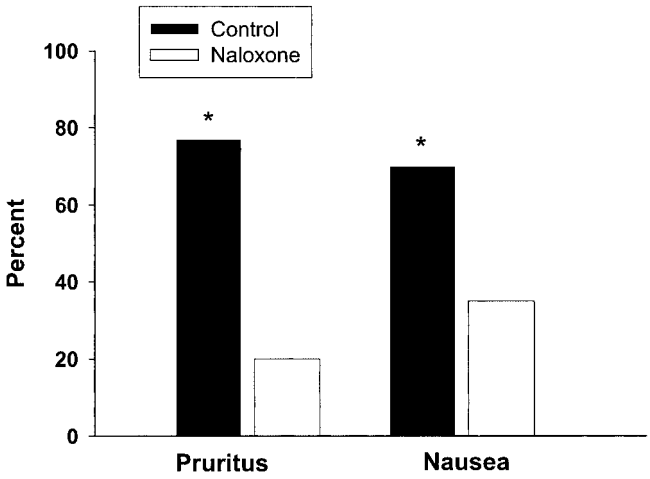

Figure 1. The incidence of pruritus and nausea is depicted. Patients receiving placebo (control) are depicted in black ■, and patients receiving small-dose naloxone are in white □. *$P < 0.05$.

alleviate symptoms. Pain scores at rest (4 ± 2 versus 3 ± 2) and with activity (coughing) (6 ± 2 versus 6 ± 2) did not differ statistically between the placebo and treatment groups, nor did morphine consumption (Fig. 2). Patients receiving placebo averaged 1.02 ± 0.41 $mg \cdot kg^{-1} \cdot d^{-1}$ of morphine versus 1.28 ± 0.61 $mg \cdot kg^{-1} \cdot d^{-1}$ in the naloxone group (Fig. 2). No patient required rescue naloxone for respiratory depression (respiratory rate <8 breaths/min, Sao_2 <90%).

Discussion

Opioid administration via a PCA system is the most rational and effective method of pain relief in children, adolescents, and adults with moderate to severe pain (7,10). Unfortunately, regardless of the method of administration, all opioids induce side effects, such as pruritus, nausea and vomiting, and urinary retention (3). Occasionally, these side effects limit the utility of opioids in the treatment of pain because some patients consider these side effects to be more distressing and debilitating than pain itself (11,12). In four previous studies, the use of small-dose opioid antagonists combined with IVPCA morphine resulted in either beneficial, adverse, or no effects (4,5,13,14). In this prospective, randomized, controlled trial, we found that a small-dose naloxone infusion (0.25 $\mu g \cdot kg^{-1} \cdot h^{-1}$) could significantly prevent opioid-induced side effects without affecting opioid-induced analgesia in children and adolescents being treated for acute, moderate to severe postoperative pain. However, we could not demonstrate an opioid-sparing effect of small-dose naloxone in our study patients.

Why would a small-dose naloxone infusion prevent opioid-induced side effects and, in some studies, paradoxically enhance analgesia, and how can the conflicting results of these different studies and ours be

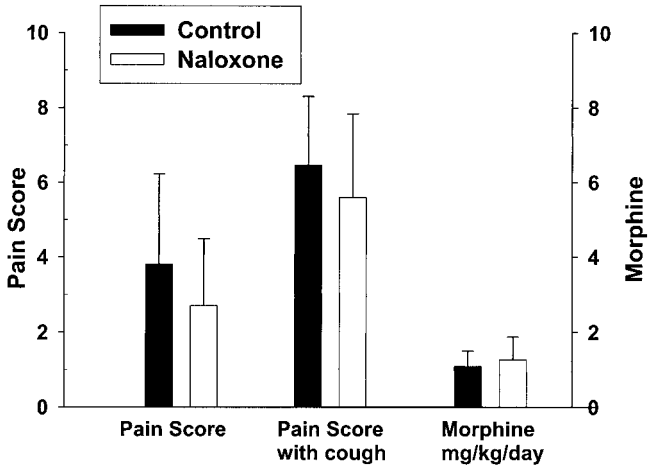

Figure 2. Pain scores at rest, with coughing, and morphine consumed in milligrams per kilogram per day are shown. Patients receiving placebo (control) are depicted in black ■ and patients receiving small-dose naloxone are in white □. Bars represent the standard error. $*P < 0.05$.

explained? All of the opioid receptors (μ, κ, and δ) are seven transmembrane domain receptors linked to heterotrimeric G proteins (15,16). The binding of opioids to these receptors initiates a range of effects including the regulation of ion channels and the triggering of complex cascades of intracellular messengers (Fig. 3). Activation of intracellular messenger pathways lead to the generation of second messengers and the regulation of protein phosphorylation and ultimately to diverse physiologic responses to extracellular stimuli. Three types of G protein are involved in the transduction of signal produced by neurotransmitter binding: G_s, $G_{i/o}$, and G_q (Fig. 3). Opioids have traditionally been thought to produce their analgesic effects via agonist binding to $G_{i/o}$-receptor–coupled complexes (17). $G_{i/o}$-coupled receptors inhibit electrical firing of neurons through the opening of inwardly rectifying K^+ channels and the closing of voltage-gated Ca^{2+} channels. They also inhibit cyclic adenosine monophosphate formation, which in turn may exert inhibitory effects on neurons. $G_{i/o}$-coupled receptors are inactivated by pertussis toxin through adenosine diphosphate-ribosylation. Crain and Shen (18–20) have proposed that opioids also bind at remarkably small doses (pico or nano-Molar concentrations) to G_s-coupled receptors. G_s-coupled receptors activate adenylyl cyclase, are coupled to an excitatory second messenger system (protein kinase A), increase Ca^{2+} ion channel conductance, close inwardly rectifying K^+ channels, and are irreversibly activated by cholera toxin (Fig. 3). Opioid binding to G_s protein–coupled receptors may therefore be responsible for the hyperalgesia occasionally reported with opioid administration and with some opioid-induced side effects, such as pruritus and nausea and vomiting. Crain and Shen (18–20) also hypothesized that small doses of opioid antagonists may decrease opioid-induced side effects and improve pain control by inhibiting only the excitatory G protein receptor complexes and leaving the inhibitory complexed receptors available for pain control. Thus, this theory would predict that, in patients receiving opioids for pain, a small-dose infusion of an opioid antagonist would prevent side effects and produce a paradoxical enhancement of analgesia. Indeed, Gan et al. (4) observed these results in adult patients being treated with IV morphine. Similarly, we saw a dramatic diminution of opioid-induced side effects but did not observe an opioid-sparing effect or paradoxical enhancement of analgesia with small-dose naloxone therapy.

The failure or success of an opioid antagonist to prevent opioid-induced side effects and to augment analgesia in some studies may be simply related to how the opioid antagonist was prepared and administered. In all studies in which the antagonist was ineffective, morphine and naloxone were mixed in saline and delivered via a PCA pump (13,14). Thus, patients received only small doses of naloxone intermittently when the PCA pump was triggered. How much naloxone was administered and how long it remained at its effector sites varied from patient to patient. Furthermore, naloxone and morphine may simply be incompatible when in a solution for a prolonged time. Conceivably, patients in these studies received less than an effective dose of naloxone to prevent side effects, and the drug was not continuously present at effector sites. However, in all studies in which an antagonist was effective, the opioid antagonist was either the longer-acting antagonist nalmefene or naloxone was administered by continuous infusion (4,5). The dose of naloxone used in this study was similar to the doses that have been reported to prevent opioid-induced side effects in adult patients (4).

We evaluated only one concentration of naloxone in this study. We could have evaluated other naloxone concentrations, or, even better, we could have used a more flexible approach in which a smaller concentration of naloxone was used prophylactically, and a larger concentration of naloxone would be introduced later if and when symptoms developed. Because we did not measure blood concentrations of either the agonist or the antagonist, we do not know if the success and failures in this study were simply pharmacokinetic; that is, the result of how much agonist and antagonist was in the blood and at the effector sites.

Patients enrolled in our study, and all of the pediatric patients we routinely clinically treat for moderate to severe pain, received PCA with a basal opioid infusion (7,10). Basal opioid infusions in the treatment of pain are controversial, in part because pain management may not be improved, and the addition of an

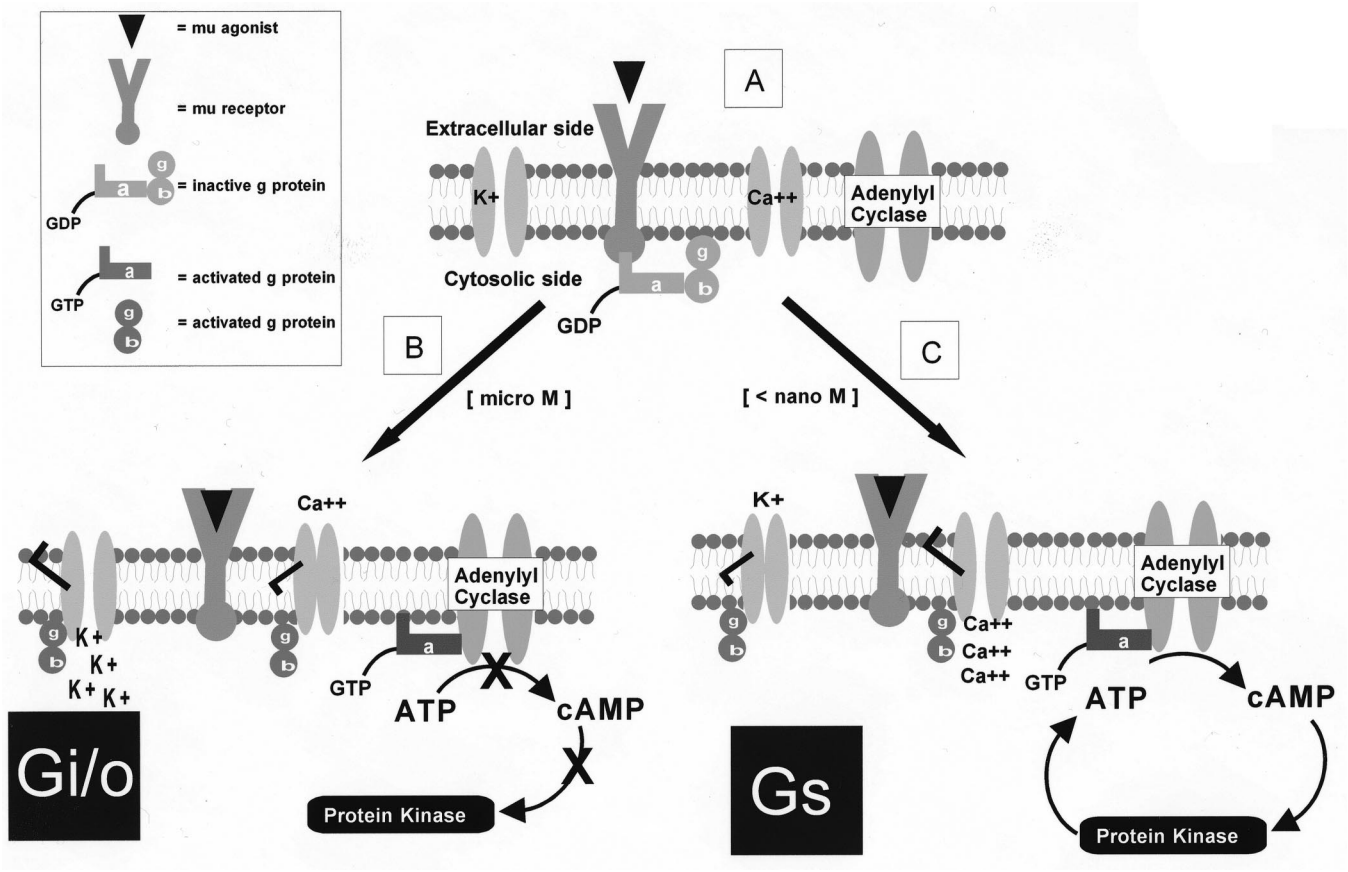

Figure 3. G protein function. The α subunits are bound by GDP, and the G protein heterotrimer is anchored to the plasma membrane by the γ subunit. (B and C) After the opioid receptor (Y) is activated by a μ agonist ligand (▼) (e.g., morphine), it physically associates with the α subunit, causing the latter to release GDP and bind GTP. The GTP binding causes the dissociation of the α subunit from the β-γ subunit and from the receptor. Free α and β-γ subunits are functionally active and directly regulate a number of effector proteins, such as ion channels, adenylyl cyclase, and phospholipase C. (B) Classically, the opioid receptor is thought to be a $G_{i/o}$-coupled receptor. Adenylyl cyclase is inhibited, the potassium channel is open, and the calcium channel is closed. (C) At pico- or nano-molar concentrations, opioid receptors are coupled to G_s proteins. Adenylyl cyclase is activated, the calcium channel is open, and the potassium channel is closed.

infusion has been associated with more oxygen desaturation and respiratory depression (21–23). However, in children and adolescents, the addition of a basal infusion has also been shown to provide improved analgesia or sleep patterns (23,24). We continue to use basal infusions because our impression is that they are clinically beneficial (7,10). We use basal infusion rates that are 30%–50% of those administered to patients who receive continuous opioid infusions as their primary method of analgesia. However, these rates are more than those generally recommended for patients receiving PCA. Whether altering or eliminating the basal infusion would affect analgesia, improve safety, change opioid consumption, impact the use of the demand component of PCA, or affect the incidence and severity of side effects are questions that require further study.

Finally, some of the side effects that are associated with opioid administration, such as urinary retention, constipation, development of tolerance, and respiratory depression, could not be evaluated in this study. Because of the nature of the surgery performed in our study population, the majority of our patients had bladder catheters and poor bowel function in the observational immediate postoperative period. Additionally, because patients were treated with IV therapy for only 2–3 days, we could not discern the development of tolerance. Finally, our study sample size was simply too small to observe any difference in the development of respiratory depression, an event that occurs in our clinical population with an incidence of one per thousand treated patients.

In conclusion, in children and adolescents, small-dose naloxone infusions ($0.25\ \mu g \cdot kg^{-1} \cdot h^{-1}$) can significantly reduce opioid-induced side effects without affecting opioid-induced analgesia. Considering the fact that 20–30 million patients a year are treated for pain in the United States, and many patients suffer because they would rather experience pain than opioid-induced side effects, these results may have an enormous impact on the provision of health care. Indeed, based on our results, we believe that when

initiating morphine IVPCA for moderate to severe postoperative pain, clinicians should strongly consider starting a concomitant small-dose naloxone infusion.

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