

Preoperative Oral Dextromethorphan Does Not Reduce Pain or Analgesic Consumption in Children After Adenotonsillectomy

John B. Rose, MD, Romulo Cuy, MD, David E. Cohen, MD, and Mark S. Schreiner, MD

Department of Anesthesiology and Critical Care Medicine, Children's Hospital of Philadelphia and The University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

In this randomized, double-blinded, placebo-controlled, prospective study, we evaluated the analgesic efficacy of dextromethorphan 0.5 mg/kg or 1.0 mg/kg PO 1 h before adenotonsillectomy in 57 children 6–12 yr of age. Anesthetic management was standardized. Morphine 0.075 mg/kg IV and acetaminophen 25–35 mg/kg PR were administered after anesthetic induction but before the start of surgery. A 4-point behavioral score (1 = asleep, 2 = awake and calm, 3 = awake and crying, 4 = thrashing) was recorded on admission to and discharge from the postanesthesia care unit (PACU). In the PACU, pain was assessed with Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) and recorded every 15 min until the patient was transferred to the day surgery unit (DSU). In the DSU, patients rated their pain using a 10-cm baseline 0–10 visual analog pain scale (VAS) every 30 min until they were discharged home. A 24-h VAS was

obtained by phone interview, and parental satisfaction was scored (yes/no) regarding their child's postoperative analgesia. Morphine 0.025 mg/kg IV was administered to children with CHEOPS score >6, who verbalized pain, or who were crying in any consecutive 5-min observation periods in the PACU. Total morphine consumption was recorded. The study groups were comparable with respect to demographic variables. We were unable to detect any differences between study groups with respect to postoperative morphine consumption, CHEOPS, behavior scores, VAS, or parental satisfaction. **Implications:** Premedication with dextromethorphan 0.5 or 1.0 mg/kg PO does not improve postoperative analgesia in school-aged children who receive preemptive morphine 0.075 mg/kg IV and acetaminophen 25–35 mg/kg PR during nitrous oxide and desflurane anesthesia for adenotonsillectomy.

(Anesth Analg 1999;88:749–53)

Adenotonsillectomy is one of the most common surgical procedures performed in children. Postoperative pain and discomfort often accompany this procedure; therefore, improved methods for providing postoperative analgesia are desirable. Dextromethorphan, a readily available nonopioid antitussive in clinical use for many years, is an *N*-methyl-D-aspartic acid (NMDA) receptor antagonist (1,2). Recently, dextromethorphan 45 mg PO administered 60 min before surgery was shown to reduce postoperative pain after tonsillectomy in adults (3). In the present study, we aimed to determine whether the administration of dextromethorphan 0.5 or 1.0 mg/kg PO 60 min prior to surgery improved analgesia, reduced opioid consumption, and resulted in greater

parental satisfaction with postoperative pain management during the first 24 h after adenotonsillectomy in 6- to 12-yr-old children. We hypothesized that there was no difference in morphine consumption, pain scores, behavior scores, or parental satisfaction with postoperative analgesia in children who received placebo versus dextromethorphan 0.5 or 1.0 mg/kg PO 60 min before adenotonsillectomy.

Methods

After institutional review board approval and informed, written parental consent, 60 children (6–12 yr old), ASA physical status I or II scheduled for adenotonsillectomy were enrolled in this investigation. A hospital pharmacist randomized participants to one of three study groups with the aid of a computer-generated random number table. The pharmacist also maintained the randomization table. All investigators and patients were blinded to the study group assignment. Subjects received either dextromethorphan

Accepted for publication December 16, 1998.

Address correspondence and reprint requests to John B. Rose, MD, Department of Anesthesiology and Critical Care Medicine, The Children's Hospital of Philadelphia, 34th & Civic Center Blvd., Philadelphia, PA 19104. Address e-mail to rose@email.chop.edu.

0.5 mg/kg, dextromethorphan 1.0 mg/kg, or placebo. All study medications were prepared by a pharmacist and administered orally 60 min before the expected start of surgery. Approximately 30 min before the induction of general anesthesia, all children received an oral preanesthetic medication consisting of midazolam 0.5 mg/kg (maximal dose 15 mg) and atropine 0.02 mg/kg. General anesthesia was induced in all children with sevoflurane and nitrous oxide in oxygen. After anesthetic induction, an IV catheter was inserted, and vecuronium 0.1 mg/kg IV was administered to facilitate endotracheal intubation. Morphine 0.075 mg/kg IV and acetaminophen 25–35 mg/kg PR were given before incision. Local anesthetic infiltration of the tonsillar beds was not performed in any patients enrolled in this study. Patients also received dexamethasone 0.5 mg/kg IV (maximal dose 10 mg) and ondansetron 0.05 mg/kg IV (maximal dose 4 mg) to reduce postoperative swelling and vomiting, as is our standard practice. General anesthesia was maintained with desflurane and nitrous oxide in oxygen. At the conclusion of surgery, children were awakened in the operating room, and their tracheas were extubated before transfer to the postanesthesia care unit (PACU).

Pain scores used included the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) and a 0–10 visual analog pain scale (VAS) consisting of a 10-cm baseline with 0 = no pain and 10 = worst imaginable pain (4,5). All postoperative behavioral and pain scores were obtained by one of two research nurses. Interrater reliability was not assessed. These same nurses conducted all postoperative phone calls. In the PACU, patients were assessed using a behavioral scale (1 = asleep, 2 = awake and calm, 3 = awake and crying, or 4 = thrashing) on admission and at discharge, and the CHEOPS every 15 min until discharge from the PACU. Additional analgesia—morphine 0.025 mg/kg IV (maximal dose 0.2 mg/kg IV)—was provided to patients with a CHEOPS score >6, who verbalized that they had throat pain, or who were crying during two consecutive 5-min observation periods. PACU nurses recorded all doses of morphine. Patients were discharged from the PACU after a minimal 1-h observation period and were admitted to the day surgery unit (DSU) to complete their recovery. In the DSU, patients were asked to rate their pain on a 0–10 VAS on admission and every 30 min until discharge while awake. Codeine 0.5 mg/kg PO was provided to patients with a VAS score >6 in the DSU, who verbalized that they had throat pain, or who were crying during two consecutive 5-min observation periods. After discharge from the DSU, parents were provided with a prescription for oral codeine 0.5 mg/kg and acetaminophen 10–15 mg/kg and with instructions to administer the analgesics every 4 h for pain. The parents of all patients were instructed to assess pain at rest 24 h after surgery with the same VAS form used in the DSU.

The parents were asked to provide this information over the telephone on the first postoperative day. They were also asked to state whether they were satisfied or dissatisfied with their child's postoperative analgesia.

The primary outcome variables were the number of patients who required morphine rescue in the PACU and the total dose of morphine required postoperatively. Secondary outcome variables included the behavior scores in the PACU, the maximal and discharge CHEOPS scores while in the PACU, the maximal and discharge VAS scores in the DSU, and the VAS score at home 24 h after surgery. The following data were also recorded for each patient: age, weight, gender, anesthesia time, surgery time, PACU length of stay, and DSU length of stay. Differences among groups were compared using an analysis of variance for interval data, the Kruskal-Wallis test for nonparametric data, and χ^2 analysis for nominal data. $P < 0.05$ was considered significant.

The sample size calculation was based on the primary end point of total morphine dose. We expected that children undergoing adenotonsillectomy would receive a total morphine dose of 0.16 ± 0.05 mg/kg IV before discharge from the PACU (6). The primary method of analysis was an analysis of variance. Using a computer software package, we determined that a sample size of 16 patients per group would permit us to detect a 25% reduction in morphine consumption compared with placebo with an 80% power while controlling for a type I error of 5% (7). A final sample size of 20 patients per study group was determined to allow for possible participant attrition.

Results

Of the 60 participants, 3 were excluded from data analysis because of protocol violations. One patient was excluded for refusal to take the study medication (dextromethorphan 0.5 mg/kg study group). Another patient was excluded for omission of the midazolam premedication (dextromethorphan 1 mg/kg study group). The third patient who was excluded from data analysis required a second operative procedure in the immediate postoperative period to control bleeding from the tonsillar fossa (placebo group).

The study groups were comparable with respect to age, weight, gender, time of study drug administration, intraoperative morphine dose, intraoperative acetaminophen dose, duration of surgery, and duration of anesthesia (Table 1). All patients were discharged from the PACU 1 h after admission. One patient in the placebo group vomited six times in the DSU, required rescue antiemetic therapy with ondansetron and trimethobenzamide hydrochloride, and had a delayed discharge time of 6 h 15 min. All other patients met discharge criteria and were discharged

Table 1. Demographic Variables, Operative Times, and Intraoperative Analgesics

	Placebo	Dextromethorphan 0.5	Dextromethorphan 1.0	P
n	19	19	19	NS
Age (yr)	7.9 ± 1.6	7.8 ± 1.7	7.9 ± 1.6	0.96
Weight (kg)	26.9 ± 5.6	26.6 ± 6.8	29.3 ± 8.1	0.41
Gender (male/female)	10/9	11/8	8/11	0.61
Study medication-induction (min)	87 ± 37	71 ± 27	84 ± 31	0.29
Anesthesia time (min)	49 ± 10	52 ± 12	53 ± 11	0.43
Surgery time (min)	19 ± 8	20 ± 6	22 ± 6	0.30
Acetaminophen (mg/kg)	27 ± 3	27 ± 3	29 ± 3	0.50
Morphine (μg/kg)	74.3 ± 8.7	74.9 ± 1.4	77.9 ± 13.9	0.51

Values are mean ± SD.

from the DSU 2 h after admission to the DSU, which is the minimal required observation period at our institution after adenotonsillectomy.

The three groups were similar with regard to the number of patients who required morphine in the PACU ($n = 13, 14,$ and $14,$ respectively; $P = 0.91$), the mean dose of morphine administered to these patients in the PACU ($44 \pm 7, 49 \pm 7,$ and $41 \pm 7 \mu\text{g}/\text{kg}$, respectively; $P = 0.75$), the maximal and discharge CHEOPS scores, and behavioral scores in the PACU (Table 2). There were no differences among the groups with respect to the mean dose of codeine administered in the DSU ($0.74 \pm 0.24, 0.69 \pm 0.13, 0.74 \pm 0.3 \text{ mg}/\text{kg}$, respectively; $P = 0.72$), the maximal and discharge VAS scores in the DSU, VAS score 24 h postoperatively, and parental satisfaction with postoperative analgesia (Table 2).

Discussion

A single dose of dextromethorphan 0.5 or 1.0 mg/kg PO administered 60 min before adenotonsillectomy had no discernable effect on the postoperative morphine requirements, pain scores, and behavior scores of 6- to 12-yr-old children. Parental satisfaction with postoperative analgesia during the first 24 h after surgery was similarly unaffected. Our findings are not consistent with an earlier report that dextromethorphan 45 mg PO reduced pain and analgesic requirements after tonsillectomy in adults (3).

Kawamata et al. (3) recognized that dextromethorphan has no direct antinociceptive effects and attributed the reduction in posttonsillectomy pain and analgesic use they observed to dextromethorphan's ability to prevent the development of central sensitization. Aside from our studying preadolescent children, several differences in study design between our study and the study of Kawamata et al. (3) may account for the differing results. First, the adults in the above-mentioned study received no other analgesics intraoperatively and were given only the nonsteroidal antiinflammatory drugs loxoprofen and diclofenac for postoperative pain. We administered dextromethorphan before surgery in combination with intraoperative morphine 0.075 mg/kg IV

and acetaminophen 25–35 mg/kg PR to determine whether the addition of dextromethorphan improved analgesia and reduced analgesic consumption after adenotonsillectomy in children. We thought that it was unethical to withhold our standard care to determine whether dextromethorphan by itself reduced pain and analgesic consumption in children. Dextromethorphan potentiates morphine-induced antinociception in laboratory animals (8), and we hoped to demonstrate a similar benefit in a clinical setting. Pain assessment in children is also more difficult than pain assessment in adults. Although we used observational and subjective pain scores as well as behavior scores to determine whether dextromethorphan reduced postoperative pain in children, other factors, such as fear, anxiety, and parental separation, which are not modified by NMDA receptor antagonism, may contribute to these scores. In the study involving adult subjects, pain was assessed daily for 7 days postoperatively. We evaluated pain only during the first 24 h postoperatively. Although Kawamata et al. (3) observed the analgesic benefit of dextromethorphan as soon as the patients were awake and alert postoperatively, it may be necessary to evaluate postoperative pain in children for a period longer than 24 h to determine whether preoperative oral dextromethorphan reduces postoperative pain. Finally, there is some evidence in adult volunteers to justify the doses of dextromethorphan (30 and 45 mg PO) used by Kawamata et al. (9). However, there are no similar studies in pediatric volunteers. We chose dextromethorphan 0.5 and 1.0 mg/kg PO based on these adult studies and on the recommended doses for antitussive therapy in children (10). It is possible that the doses we used were too small to produce an analgesic benefit in children.

NMDA receptor antagonism inhibits windup or central hypersensitivity of dorsal horn neurons in response to noxious stimulation (11). Dextromethorphan, an NMDA receptor antagonist, has been shown to reduce secondary hyperalgesia but to have no effect on primary hyperalgesia in healthy adult male volunteers (9,12). In one study, dextromethorphan 30 or 45 mg PO reduced secondary hyperalgesia but had no effect on primary hyperalgesia in response to electric

Table 2. Patients Who Required MSO₄ Rescue in the PACU, Morphine Administered, CHEOPS and Behavioral Scores in the PACU, VAS in the DSU and at Home, and Parental Satisfaction with Analgesia

	Placebo	Dextromethorphan 0.5	Dextromethorphan 1.0	P
MSO ₄ rescue (n)	13	14	14	0.91
Morphine (μg/kg)	44 ± 7	49 ± 7	41 ± 7	0.75
Behavior score				
Admission	2 (1-3)	2 (1-3)	2 (1-3)	0.81
Discharge	2 (1-2)	2 (2)	2 (2)	0.84
CHEOPS				
Maximum	8 (6-9)	9 (6-10)	8 (6-10)	0.60
Discharge	6 (6)	6 (6)	6 (6)	0.74
VAS				
DSU, maximum	6 (5-10)	5 (5-10)	6 (5-10)	0.88
DSU, discharge	2 (0-5)	2 (0-5)	3 (0-5)	0.99
Home, 24 h	5 (3-7)	5 (2-6)	5 (1-6)	0.47
Parental satisfaction (yes/no)	16/3	16/3	18/1	0.52

Values are median (interquartile range).

PACU = postanesthesia care unit, CHEOPS = Children's Hospital of Eastern Ontario Pain Scale, VAS = visual analog scale, DSU = day surgery unit.

shocks or 52°C heat pulses (9). More recently, adult volunteers who received dextromethorphan 60 or 120 mg PO versus placebo experienced a reduction in the magnitude of secondary hyperalgesia to pinprick after burn injuries (12). However, dextromethorphan did not attenuate primary hyperalgesia, as measured by pain during heat stimulation, or heat-pain-detection thresholds in undamaged skin (12). Other investigators have been unable to demonstrate that dextromethorphan, in clinically relevant doses, has any effect on primary or secondary hyperalgesia (13,14).

Dextromethorphan's efficacy as an analgesic adjuvant has been studied in several clinical settings with mixed results. The addition of dextromethorphan 40.5 or 81 mg PO daily as an analgesic adjuvant had no effect on pain intensity, pain relief, or global rating of treatment in 19 adult patients with chronic neuropathic pain (15). However, when the dose of dextromethorphan was increased to the highest level without interrupting normal patient activities, dextromethorphan (mean dose 381 mg/d) significantly reduced pain associated with diabetic neuropathy but not postherpetic neuralgia (16). The occurrence of side effects, including sedation and ataxia, during the escalation of dextromethorphan dosing resulted in 5 of 31 patients dropping out of this study.

Further investigations are required to determine whether larger doses or repeated doses of dextromethorphan attenuate postoperative pain in children. However, undesirable side effects of dextromethorphan, including sedation and ataxia, are common in adults when the dose is increased above that recommended for antitussive therapy and may limit the usefulness of these strategies in children. Furthermore, behavioral disturbances, respiratory depression, and acute dystonic reactions have been reported in children who ingested cough and cold syrups containing dextromethorphan (9,17,18).

In conclusion, dextromethorphan 0.5 and 1.0 mg/kg PO administered 1 h before adenotonsillectomy in 6- to 12-yr-old children whose general anesthetic was supplemented with morphine 0.075 mg/kg IV and acetaminophen 25-35 mg/kg PR had no effect on postoperative morphine requirements, pain and behavior scores, or parental satisfaction with postoperative analgesia in the first 24 h after surgery.

References

1. Netzer R, Pflimlin P, Trube G. Dextromethorphan blocks N-methyl-D-aspartate-induced currents and voltage-operated inward currents in cultured cortical neurons. *Eur J Pharmacol* 1993;238:209-16.
2. Grattan TJ, Marshall AE, Higgins KS, Morice AH. The effect of inhaled and oral dextromethorphan on citric acid induced cough in man. *Br J Clin Pharmacol* 1995;39:261-3.
3. Kawamata T, Omote K, Kawamata M, Namiki A. Premedication with oral dextromethorphan reduces postoperative pain after tonsillectomy. *Anesth Analg* 1998;86:594-7.
4. Tyler DC, Tu A, Douthit J, Chapman CR. Toward validation of pain measurement tools for children: a pilot study. *Pain* 1993; 52:301-9.
5. McGrath PA. Pain in the pediatric patient: practical aspects of assessment. *Pediatr Ann* 1995;24:126-33.
6. Rose JB, Martin TM. Posttonsillectomy vomiting. Ondansetron or metoclopramide during paediatric tonsillectomy: are two doses better than one? *Paediatr Anaesth* 1996;6:39-44.
7. Dallal GE. PC—size: a program for sample size determinations. *Am Stat* 1986;40:52.
8. Plesan A, Hedman U, Xu XJ, Wiesenfeld-Hallin Z. Comparison of ketamine and dextromethorphan in potentiating the antinociceptive effect of morphine in rats. *Anesth Analg* 1998;86:825-9.
9. Price DD, Mao J, Frenk H, Mayer DJ. The N-methyl-D-aspartate receptor antagonist dextromethorphan selectively reduces temporal summation of second pain in man [see comments]. *Pain* 1994;59:165-74.
10. Anonymous. Use of codeine- and dextromethorphan-containing cough remedies in children. American Academy of Pediatrics, Committee on Drugs. *Pediatrics* 1997;99:918-20.
11. Woolf CJ, Thompson SW. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation: implications for the treatment of post-injury pain hypersensitivity states. *Pain* 1991;44:293-9.

12. Ilkjaer S, Dirks J, Brennum J, et al. Effect of systemic N-methyl-D-aspartate receptor antagonist (dextromethorphan) on primary and secondary hyperalgesia in humans. *Br J Anaesth* 1997;79:600-5.
13. Kinnman E, Nygard EB, Hansson P. Effects of dextromethorphan in clinical doses on capsaicin-induced ongoing pain and mechanical hypersensitivity. *J Pain Symptom Manage* 1997;14:195-201.
14. Kauppila T, Gronroos M, Pertovaara A. An attempt to attenuate experimental pain in humans by dextromethorphan, an NMDA receptor antagonist. *Pharmacol Biochem Behav* 1995;52:641-4.
15. McQuay HJ, Carroll D, Jadad AR, et al. Dextromethorphan for the treatment of neuropathic pain: a double-blind randomised controlled crossover trial with integral n-of-1 design. *Pain* 1994;59:127-33.
16. Nelson KA, Park KM, Robinovitz E, et al. High-dose oral dextromethorphan versus placebo in painful diabetic neuropathy and postherpetic neuralgia. *Neurology* 1997;48:1212-8.
17. Gaudins A, Fern RP. Acute dystonia in a child associated with therapeutic ingestion of a dextromethorphan containing cough and cold syrup [letter; comment]. *J Toxicol Clin Toxicol* 1996;34:351-2.
18. Warden CR, Diekema DS, Robertson WO. Dystonic reaction associated with dextromethorphan ingestion in a toddler. *Pediatr Emerg Care* 1997;13:214-5.