

# The Interaction Effect of Perioperative Cotreatment with Dextromethorphan and Intravenous Lidocaine on Pain Relief and Recovery of Bowel Function After Laparoscopic Cholecystectomy

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Both dextromethorphan (DM) and IV lidocaine improve postoperative pain relief. In the present study, we evaluated the interaction of DM and IV lidocaine on pain management after laparoscopic cholecystectomy (LC). One-hundred ASA physical status I or II patients scheduled for LC were randomized into four equal groups to receive either: (a) chlorpheniramine maleate (CPM) intramuscular injection (IM) 20 mg and IV normal saline (N/S) (group C); (b) DM 40 mg IM and IV N/S (group DM); (c) CPM 20 mg IM and IV lidocaine  $3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  (group L); or (d) DM 40 mg IM and IV lidocaine (group DM+L). All treatments were administered 30 min before skin incision. Analgesic effects were

evaluated using visual analog scale pain scores at rest and during coughing, time to meperidine request, total meperidine consumption, and the time to first passage of flatus after surgery. Patients of the DM+L group exhibited the best pain relief and fastest recovery of bowel function among groups. Patients in the DM and L groups had significantly better pain relief than those in the C group. The results showed an additional effect on pain relief and a synergistic effect on recovery of bowel function when DM was combined with IV lidocaine after LC.

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**M**any patients still suffer from moderate to severe pain after laparoscopic cholecystectomy (LC) (1). Different treatments have been used to relieve pain, including nonsteroidal antiinflammatory drugs, opioids, and local anesthetics, but none has been consistently satisfactory. This may be because post-LC pain results from a combination of inflammatory, incisional somatic, and visceral components (2).

In previous studies, we had found that preincisional IM treatment with 40 mg of dextromethorphan (DM) provided good pain management in patients who underwent upper abdominal surgery, LC, and modified

radical mastectomy by diminishing central sensitization (3–5). Multimodal analgesia has become a current trend in postoperative pain management (6). This implies that a single antagonist may not be sufficient to prevent postoperative pain if other pathways are not blocked.

Lidocaine may provide a multimodal approach to pain management for the post-LC patient. Groudine et al. (7) studied IV lidocaine administration ( $3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ) in patients undergoing radical retropubic prostatectomy and concluded that lidocaine reduced the neural response to pain by blockade or inhibition of nerve conduction. In addition to blocking nerve transmission, lidocaine has significant antiinflammatory properties (8). Moreover, Ness (9) found that IV lidocaine might be an effective modality for treating visceral pain. Therefore, lidocaine is also a potential drug for treating the complex pain property after LC.

The aim of the present study was to evaluate the interaction effect of combination preincisional DM and IV lidocaine on pain management after LC.

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## Methods

This study was approved by our IRB. Written informed consent was obtained from all patients in the study. One-hundred ASA physical status I or II patients scheduled for elective LC were included and randomly divided into four groups. The study was double-blind and randomized with a computer program. The study drugs (chlorpheniramine maleate [CPM], DM, lidocaine, and normal saline [N/S]) were prepared by the hospital pharmacy in identical containers marked with the name of the project, the investigator's name, administer routes, and consecutive numbers. Patients were excluded if they had clinically diagnosed acute pancreatitis, were scheduled to undergo any surgical procedure expected to produce more trauma than LC alone, had acute preoperative pain other than biliary colic, required chronic pain treatment, or had current or recent cancer or any condition that would contraindicate participation in a surgical study of this nature. Patients with contraindications for lidocaine or who had received opioids or nonsteroidal antiinflammatory drugs within 1 wk were excluded. Patients were assessed for eligibility within 14 days before surgery, provided a full medical history, and underwent complete physical examination and laboratory tests. Preoperatively, all patients were instructed in the use of a visual analog scale (VAS) to measure pain scores for pain assessment.

Based on retrospective data from our institution in the same surgical population, a power analysis was performed using reduction in meperidine consumption as the primary outcome variable. It is clinically meaningful because reduced opioid consumption implied that patients exhibited lower pain scores and less opioid-related side effects. We calculated a sample size so that a between-group mean difference in meperidine consumption of 25 mg would permit a one-tailed type I error rate of  $\alpha = 0.05$  with a power of 80%. This analysis indicated that a sample size of at least 20 patients per group was required.

The doses of IV lidocaine ( $3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ) and DM were chosen on the basis of previous studies (7,10,11). The dose of 40 mg of DM containing 20 mg of CPM was used (3–5) because of the available formulation of DM so that 1 ampoule of DM (10 mg) contains 5 mg of CPM. DM was given IM because the bioavailability of oral DM is only 10% (12), whereas the bioavailability after an IM injection is similar to that after an IV injection, with almost the same rapid onset. Dextrophan, the liver metabolite of DM, may be responsible for most of the side effects attributed to DM, although a large dose of IV DM leads to hypotension and tachycardia. Therefore, IM administration may provide a better alternative to an oral or IV administration route, with rapid onset in acute pain

states, fewer side effects, and decreased risk of aspiration in patients undergoing general anesthesia.

Patients in the group DM+L received DM IM and IV lidocaine; patients in the group DM received DM IM and an equal IV volume of N/S; patients of the group L received 20 mg of CPM IM and IV lidocaine; patients of the group C received 20 mg of CPM IM and an equal IV volume of N/S. All treatments were administered 30 min before skin incision, and lidocaine or N/S was infused with a pump throughout the surgery.

For all patients, general anesthesia was induced with IV fentanyl ( $2 \mu\text{g}/\text{kg}$ ), atracurium (5 mg), and thiopental (3–5 mg/kg). Tracheal intubation was facilitated with succinylcholine (1.5 mg/kg). Anesthesia was maintained with desflurane in oxygen (300 mL/min) via a total closed-circuit system. Atracurium was used for muscle relaxation. The end-tidal desflurane concentration was controlled to maintain the systolic blood pressure within the range of 20% of the basal systolic blood pressure. End-tidal desflurane concentrations were monitored continuously and recorded at 30 min after the induction, 30 min after skin incision, and at the end of the surgical procedure. Respiratory frequency and tidal volume were adjusted to maintain the end-tidal carbon dioxide level at 35–45 mm Hg. Esophageal temperature was maintained at  $35^{\circ}\text{C}$ – $37^{\circ}\text{C}$ . No additional opioids were given during the operation. At the end of surgery, residual neuromuscular blockade was antagonized with edrophonium (0.8 mg/kg) and atropine (0.01 mg/kg), and the endotracheal tube was removed when the patient started to breathe spontaneously and smoothly.

A meperidine (1 mg/kg) IM injection was used for postoperative pain relief, if requested, because it has been widely used for pain relief after LC in our country. In most LC patients, one or two doses of meperidine can provide adequate pain relief, so this treatment was preferable to patient-controlled analgesia. A 10-cm VAS (with end-points labeled “no pain” and “worst possible pain”) was used to assess pain intensity at rest and during coughing at 1, 2, 4, 12, 24, and 48 h after completion of surgery. We recorded the time to first meperidine injection, total meperidine consumption, the first time to the passage of flatus by patients' self-report, and side effects related to meperidine (drowsiness, dizziness, nausea, and vomiting), CPM (vertigo, drowsiness, headache, nausea, blurred vision, and weakness), DM (nausea, vomiting, dizziness, hot flashes, drowsiness, heartburn, and headache), and lidocaine (cardiac arrhythmia, light headed, drowsiness, perioral numbness, metal taste, dryness of the mouth, nausea, muscular twitch, tinnitus, and visual disturbances) for 48 h after the operation. All observations were made by a study nurse. Side effects were treated as required.

**Table 1.** Demographic Data and Operation Duration

	Group C (n = 25)	Group DM (n = 25)	Group L (n = 25)	Group DM + L (n = 25)
Age (yr)	51.4 ± 8.4	52.4 ± 10.2	51.8 ± 7.2	50.9 ± 9.6
Sex (M/F)	11/14	10/15	10/15	11/14
Weight (kg)	60.8 ± 7.3	59.2 ± 6.0	61.8 ± 7.1	60.1 ± 7.5
Height (cm)	162.9 ± 6.2	161.4 ± 5.8	162.9 ± 4.4	162.3 ± 4.4
Operation duration (min)	81.0 ± 8.4	81.8 ± 8.6	81.4 ± 9.1	81.2 ± 8.5
End-tidal of desflurane	6.8% ± 0.3%	6.7% ± 0.4%	5.1% ± 0.3%*	5.1% ± 0.3%*

Except for sex, all data are presented as the mean ± SD.

\*  $P < 0.05$  as compared with group C and dextromethorphan (DM). Group C = chlorpheniramine maleate (CPM) 20 mg IV + equal IV volume of normal saline (N/S); Group DM = DM 40 mg IV and equal IV volume of N/A; Group lidocaine (L) = CPM 20 mg IV and IV lidocaine ( $3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ); Group DM + L = DM 40 mg IV and IV lidocaine.

All data are expressed as the mean ± SD. Differences in the demographic data and clinical characteristics among the subjects in the four groups were evaluated by one-way analysis of variance, and Scheffé tests were used to compare differences among groups. The  $\chi^2$  test was used to evaluate differences in the incidence of requests for meperidine and the meperidine-related side effects among groups. The log-rank test and Cox proportional hazards model were used to compare differences in the duration to the first meperidine injection and first passage of flatus. To evaluate the enhanced effect of the combination of the two treatments, an interaction term was introduced into either the multiple regressions (analysis for total meperidine consumption) or Cox proportional hazards model (analysis for time to first meperidine injection and first passage of flatus). All statistical analyses were two-tailed. Statistical significance was accepted at the 5% probability level.

## Results

The groups were similar in age, body weight, height, men-to-women ratio, and duration of surgery (Table 1). Average end-tidal desflurane concentration was significantly smaller in both lidocaine-treated groups (Table 1) because of the analgesic and vasodilatation effects of the lidocaine. The mean time to the first meperidine injection (h) showed a significant difference between groups DM+L and L or C ( $P < 0.001$ ) and groups DM and C ( $P < 0.05$ ; Table 2). Meperidine consumption was significantly less over the 2-day observation period for groups DM+L, DM, and L compared with group C ( $P < 0.001$ ) and group DM+L compared with group L ( $P < 0.05$ ; Table 2). There was a significant decrease in the incidence of patients requiring meperidine injection among the groups DM+L and DM, L, or C ( $P < 0.001$ ), DM and C ( $P < 0.05$ ), and L and C ( $P < 0.05$ ) (Table 2). There were also small but significant differences in VAS among the groups at rest and during coughing. Figure 1 shows that VAS scores at rest were significantly lower in the

DM+L group compared to group C for the first 12 h. VAS scores during coughing were significantly lower for the same comparison for the first 24 h. For the single therapy groups DM and L, VAS scores were significantly lower at rest for 2 h, whereas coughing VAS scores were significantly lower for 24 h and 12 h compared with control. The combined therapy group DM+L showed significantly lower VAS scores at rest compared with either single-treatment group (DM or L) for 4 h, whereas coughing VAS scores were significantly lower for 24 h compared to the single-therapy groups. Patients in the group DM+L exhibited the fastest return of bowel function among groups ( $P < 0.001$  compared to group C;  $P < 0.05$  compared to groups DM and L) (Table 2). There were significant differences in meperidine-associated nausea, vomiting, dizziness, or headache between DM+L and C ( $P < 0.001$ ) or L ( $P < 0.05$ ) and between DM and C ( $P < 0.001$ ) (Table 2). Six and three patients were treated with IV prochlorperazine 5 mg for vomiting in the control and lidocaine groups, respectively. No DM- or CPM-related side effects were observed during the 48-h observation period. All patients who started on the IV lidocaine infusion finished their full course of the drug. No patient experienced an identifiable adverse event related to the lidocaine infusion, except that an occasional arrhythmia with stable vital signs was noted in one patient in both groups L and DM+L.

Both DM and lidocaine had a significant effect on the time to first trigger of meperidine (DM:  $\beta = -1.30$ ;  $P = 0.001$ ; and L:  $\beta = -1.03$ ;  $P = 0.004$ ), total meperidine consumption (DM:  $\beta = -0.57$ ;  $P < 0.001$ ; and L:  $\beta = -0.38$ ;  $P = 0.002$ ), and the reduction in meperidine requirement (DM:  $\beta = -1.90$ ;  $P < 0.005$ ; and L:  $\beta = -1.58$ ;  $P = 0.02$ ); however, no significant synergistic or antagonistic interaction between DM and lidocaine was found (DM × L;  $\beta = -0.12$ ;  $P = 0.858$ ;  $\beta = 14.7$ ;  $P = 0.372$ ;  $\beta = 1.7$ ;  $P = 0.866$ , respectively) (Table 3). Therefore, an additional interaction was observed on the coadministration of DM and lidocaine on the time to first trigger of meperidine, total meperidine consumption, and percentage of patients requiring meperidine.

**Table 2.** Postoperative Analgesia, Recovery, and Incidence of Side Effects

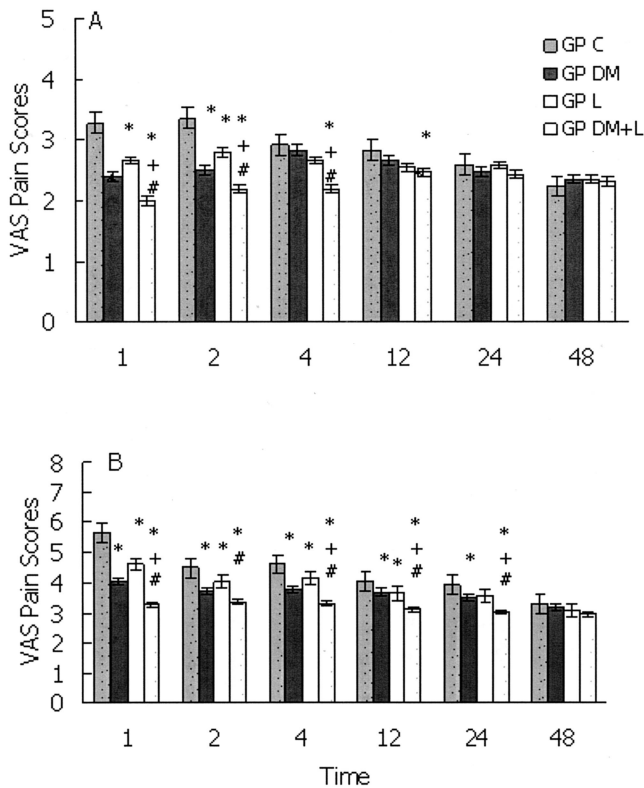
	Group C (n = 25)	Group DM (n = 25)	Group L (n = 25)	Group DM + L (n = 25)
Time to first meperidine injection (h) <sup>a</sup>	8.2 ± 17.7	27.4 ± 23.8*	21.7 ± 23.8	41.8 ± 14.4*†
Total meperidine consumption (mg)	87.3 ± 47.7	31.6 ± 38.3*	50.4 ± 49.7*	9.4 ± 22.0*†
Meperidine requirement (%)	84.0	44.0*	52.0*	16.0*††
Times of first passage of flatus (h)	22.9 ± 1.8	22.2 ± 1.5	22.1 ± 1.6	13.4 ± 2.1*††
Meperidine-related side effects	10	3*	7	1*†

Values are mean ± SD or number of patients or percentage.

<sup>a</sup> If patients did not receive a meperidine injection during the 2-day observation, the time to first meperidine injection was recorded as 48 h. DM = dextromethorphan; N/S = normal saline; CPM = chlorpheniramine maleate; L = lidocaine.

Group C = CPM 20 mg IV + equal IV volume of N/S; Group DM = DM 40 mg IV and equal IV volume of N/S; Group L = CPM 20 mg IV and IV lidocaine (3 mg · kg<sup>-1</sup> · h<sup>-1</sup>); Group DM + L = DM 40 mg IV and IV lidocaine.

\* P < 0.001 compared with the group C; † P < 0.05 compared with the group L; †† P < 0.05 compared with the group DM.



**Figure 1.** Visual analog scale (VAS) pain scores at rest (A) and during coughing (B). Values are mean ± SD. \*P < 0.05 as compared to the group C; †P < 0.05 as compared to the group dextromethorphan (DM); #P < 0.05 as compared to the group lidocaine (L). Group C: chlorpheniramine maleate (CPM) 20 mg IM + equal IV volume of normal saline (N/S); Group DM: DM 40 mg IM and equal IV volume of N/S; Group L: CPM 20 mg IM and IV lidocaine (3 mg · kg<sup>-1</sup> · h<sup>-1</sup>); Group DM+L: DM 40 mg IM and IV lidocaine.

## Discussion

The present study showed that coadministration of preincisional DM IM 40 mg plus IV lidocaine (3 mg · kg<sup>-1</sup> · h<sup>-1</sup>) provided superior postoperative pain relief compared with either treatment alone. Our study also suggested that the effect between the drugs was additive because the combined therapy group had the longest time period before the first request for

meperidine, the fewest patients requiring meperidine, the lowest VAS pain scores, and the least meperidine consumption. The most interesting finding is that there was a significant synergistic interaction between DM and lidocaine (DM × L; β = -7.92; P < 0.001) on recovery of bowel function; however, both DM and lidocaine had no significant effect by themselves (DM: β = -0.09; P = 0.152; and L: β = -0.09; P = 0.112) (Table 3).

New non-opioid strategies of pain control during the perioperative period have emerged recently. DM is a noncompetitive N-methyl-D-aspartic acid (NMDA) receptor antagonist. It is rapidly metabolized in the liver, where it is transformed to dextrorphan, an active and more potent NMDA receptor antagonist (13). The side effects of DM documented in clinical studies might be mediated by this metabolite acting at the phencyclidine receptor site rather than by DM itself (14). DM has a long history of clinical use with an established safety record (15). The results of previous studies that used DM to block or attenuate the central sensitization induced by noxious stimulation are controversial (3–5,16–19). The present results are compatible with those of Helmy and Bali (17), Weinbroum et al. (16), and our previous studies (3–5), which showed that preoperative DM treatment provided a better analgesic effect and might have prevented the sensitization of nociceptive neurons in the spinal cord. DM was shown to have a role in alleviating both acute somatic and visceral pain and has been gaining greater clinical acceptance as a multimodal analgesic adjuvant to achieve better pain relief by preventing central nervous system sensitization (20). The failure of some studies to demonstrate a better analgesic effect of DM may be explained by insufficient afferent blockade required to prevent central sensitization because of the use of small doses, oral administration, improper timing of administration in acute pain, and its use in neuropathic pain syndromes after the establishment of central sensitization (18,19).

IV lidocaine suppresses neuronal excitability in dorsal horn neurons, depresses spike activity, amplitude, and

**Table 3.** Evaluation of the Interaction Effect of Combination of Dextromethorphan (DM) and Lidocaine (L)

	Main effect (regression coefficient)				Interaction	
	DM <sup>a</sup>		Lidocaine <sup>b</sup>		(DM × Lidocaine)	
	$\beta$	<i>P</i> -value	$\beta$	<i>P</i> -value	$\beta$	<i>P</i> -value
Time to first trigger of meperidine <sup>c</sup>	-1.30	0.001	-1.03	0.04	-0.12	0.858
Total meperidine consumption <sup>d</sup>	-0.57	<0.001	-0.38	0.002	14.7	0.372
Meperidine Requirement <sup>d</sup>	-1.90	0.005	-1.58	0.02	0.17	0.866
Time to first passage of flatus <sup>e</sup>	-0.09	0.152	-0.09	0.112	-7.92	<0.001

<sup>a</sup> Patients who receiving DM regimen (*n* = 50, including patients in groups DM and DM + L).

<sup>b</sup> Patients who receiving Lidocaine (*n* = 50, including patients in groups L and DM + L).

<sup>c</sup> Cox's proportional hazards model was used for analysis.

<sup>d</sup> The values were transformed into natural logarithms and multiple regression was used for analysis.

\* A *P*-value < 0.05 indicates a synergistic or antagonistic interaction of DM and lidocaine.

Group C = chlorpheniramine maleate (CPM) 20 mg IV + equal IV volume of normal saline (N/S); Group DM = DM 40 mg IV and equal IV volume of N/S; Group L = CPM 20 mg IV and IV lidocaine (3 mg · kg<sup>-1</sup> · h<sup>-1</sup>); Group DM + L = DM 40 mg IV and IV lidocaine.

conduction time in both myelinated A- $\delta$  and unmyelinated C fibers (21), decreases the neural response to postoperative pain by blockade or inhibition of nerve conduction (7), suppresses central sensitization (10,11), inhibits spinal visceromotor neurons (9), possesses an antiinflammatory effect (8), and reduces postoperative pain in the clinical setting (7,10,21). However, other clinical studies suggested that lidocaine has no beneficial effect (22,23). The discrepancy between these results might be due to the differences in the dosage of lidocaine and the timing of its administration. In addition, the modes and patterns of peripheral and central sensitization might be different between types and regions of surgery. Our study showed that lidocaine is an effective drug for treating pain after LC. Nagy and Woolf (24) observed that local anesthetics could selectively reduce C fiber-evoked neuronal activity in rats and subsequently reduce the nociceptive transmission in the spinal cord by decreasing NMDA receptor activity. Imamachi et al. (25) demonstrated that NMDA receptor antagonists could interact with lidocaine synergistically at the spinal level in rats. In previous studies, the preemptive epidural analgesic regimen combining morphine, ketamine, and local anesthetics provided superior analgesia compared with morphine with local anesthetics after upper abdominal surgery (26). Our results were consistent with many clinical studies showing an additive analgesic effect of DM and lidocaine (16,17), resulting in diminished pain and opioid consumption. However, the meperidine-sparing effect of DM plus lidocaine was manifested in the first 12 hours after surgery. Thus, further study is required to assess whether postoperative infusions should be continued for longer periods of time or just immediately after surgery.

Rimback et al. (21) and Groudine et al. (7) showed that continuous IV lidocaine provided a faster return of bowel function after surgery. In the present study, we could not demonstrate that lidocaine improved bowel function. These conflicting results may be due to differences in the total dosage of lidocaine or the smaller extent and severity of our surgical procedure.

DM antagonizes the contractility of guinea pig ileum (27), which might cause delayed recovery of bowel function. We cannot demonstrate a negative role of DM on bowel function. DM's lack of effect on bowel function might have been caused by attenuation of nociceptive afferent nerve input resulting in reduced opioid consumption. However, we showed an unexpected improvement in bowel function by the combination of DM and lidocaine over the DM or lidocaine groups. Because both pain and opioid administration can diminish bowel function and cause postoperative ileus, improved analgesia and reduced opioid administration by themselves contribute to minimize postoperative ileus. We postulated that diminished pain and opioid consumption might further contribute a synergistic effect to the recovery of bowel function.

The limitation of our study was that patients in the control group received CPM 20 mg, which might have provided a sedative effect and delayed the first trigger time. However, all patients in the study groups received CPM 20 mg, and the first trigger times were longer than the control group. Therefore, the effect of CPM could not account for our results. We did not compare multiple dosages of DM and lidocaine because the dosages of DM 40 mg (3-5) and lidocaine (7,10,11) were well established in previous studies. Finally, we also did not measure the serum levels of lidocaine because it was well studied (7).

Taken together, we demonstrated that the combination of perioperative IM DM 40 mg with IV lidocaine (3 mg · kg<sup>-1</sup> · h<sup>-1</sup>) provides an addition effect on postoperative pain relief and a synergistic effect to accelerate recovery of bowel function after LC.

## References

- Joshi GP, Viscusi ER, Gan TJ, et al. Effective treatment of laparoscopic cholecystectomy pain with intravenous followed by oral COX-2 specific inhibitor. *Anesth Analg* 2004;98:336-42.

2. Neudecker J, Sauerland S, Neugebauer E, et al. The European Association for Endoscopic Surgery clinical practice guideline on the pneumoperitoneum for laparoscopic surgery. *Surg Endosc* 2002;16:1121-43.
3. Wu CT, Yu JC, Liu ST, et al. Preincisional dextromethorphan treatment for postoperative pain management after upper abdominal surgery. *World J Surg* 2000;24:512-7.
4. Wu CT, Yu JC, Yeh CC, et al. Preincisional dextromethorphan treatment decreases postoperative pain and opioid requirement after laparoscopic cholecystectomy. *Anesth Analg* 1999;88:1331-4.
5. Wong CS, Wu CT, Yu JC, et al. Preincisional dextromethorphan decreases postoperative pain and opioid requirement after modified radical mastectomy. *Can J Anaesth* 1999;46:1122-6.
6. Kehlet H, Wilmore DW. Multimodal strategies to improve surgical outcome. *Am J Surg* 2002;183:630-41.
7. Groudine SB, Fisher HA, Kaufman RP Jr, et al. Intravenous lidocaine speeds the return of bowel function, decreases postoperative pain, and shortens hospital stay in patients undergoing radical retropubic prostatectomy. *Anesth Analg* 1998;86:235-9.
8. Hollmann MW, Durieux ME. Local anesthetics and the inflammatory response: a new therapeutic indication? *Anesthesiology* 2000;93:858-75.
9. Ness TJ. Intravenous lidocaine inhibits visceral nociceptive reflexes and spinal neurons in the rat. *Anesthesiology* 2000;92:1685-91.
10. Kawamata M, Takahashi T, Kozuka Y, et al. Experimental incision-induced pain in human skin: effects of systemic lidocaine on flare formation and hyperalgesia. *Pain* 2002;100:77-89.
11. Dirks J, Fabricius P, Petersen KL, et al. The effect of systemic lidocaine on pain and secondary hyperalgesia associated with the heat/capsaicin sensitization model in healthy volunteers. *Anesth Analg* 2000;91:967-72.
12. Wills RJ, Martin KS. Dextromethorphan/dextrorphan disposition in rat plasma and brain. *Pharm Res* 1988;5:S193.
13. Church J, Lodge D, Berry SC. Differential effects of dextrorphan and levorphanol on the excitation of rat spinal neurons by amino acids. *Eur J Pharmacol* 1985;111:185-90.
14. Musacchio JM, Klein M, Canoll PD. Dextromethorphan and sigma ligands: common sites but diverse effects. *Life Sci* 1989;45:1721-32.
15. Bem JL, Peck R. Dextromethorphan: an overview of safety issues. *Drug Saf* 1992;7:190-9.
16. Weinbroum AA, Bender B, Nirkin A, et al. Dextromethorphan-associated epidural patient-controlled analgesia provides better pain- and analgesics-sparing effects than dextromethorphan-associated intravenous patient-controlled analgesia after bone-malignancy resection: a randomized, placebo-controlled, double-blinded study. *Anesth Analg* 2004;98:714-22.
17. Helmy SA, Bali A. The effect of the preemptive use of the NMDA receptor antagonist dextromethorphan on postoperative analgesic requirements. *Anesth Analg* 2001;92:739-44.
18. Kawamata T, Omote K, Kawamata M, Namiki A. Premedication with oral dextromethorphan reduces postoperative pain after tonsillectomy. *Anesth Analg* 1998;86:594-7.
19. McConaghy PM, McSorley P, McCaughey W, Campbell WI. Dextromethorphan and pain after total abdominal hysterectomy. *Br J Anaesth* 1998;81:731-6.
20. Weinbroum AA, Rudick V, Paret G, Ben-Abraham R. The role of dextromethorphan in pain control. *Can J Anaesth* 2000;47:585-96.
21. Rimback G, Cassuto J, Tolleson PO. Treatment of postoperative paralytic ileus by intravenous lidocaine infusion. *Anesth Analg* 1990;70:414-9.
22. Birch K, Jorgensen J, Chraemmer-Jorgensen B, Kehlet H. Effect of i.v. lignocaine on pain and the endocrine metabolic responses after surgery. *Br J Anaesth* 1987;59:721-4.
23. Insler SR, O'Connor M, Samonte AF, Bazaral MG. Lidocaine and the inhibition of postoperative pain in coronary artery bypass patients. *J Cardiothorac Vasc Anesth* 1995;9:541-6.
24. Nagy I, Woolf CJ. Lignocaine selectively reduces C fibre-evoked neuronal activity in rat spinal cord *in vitro* by decreasing N-methyl-D-aspartate and neurokinin receptor-mediated post-synaptic depolarizations: implications for the development of novel centrally acting analgesics. *Pain* 1996;64:59-70.
25. Imamachi N, Saito Y, Hara K, et al. The non-NMDA glutamate receptor antagonist CNQX augments lidocaine antinociception through a spinal action in rats. *Anesth Analg* 1999;89:416-21.
26. Wu CT, Yeh CC, Yu JC, et al. Pre-incisional epidural ketamine, morphine and bupivacaine combined with epidural and general anaesthesia provides pre-emptive analgesia for upper abdominal surgery. *Acta Anaesthesiol Scand* 2000;44:63-8.
27. Kachur JF, Morgan DW, Gaginella TS. Effect of dextromethorphan on guinea pig ileal contractility *in vitro*: comparison with levomethorphan, loperamide and codeine. *J Pharmacol Exp Ther* 1986;239:661-7.