

## Dextromethorphan and pain after total abdominal hysterectomy

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### Summary

Dextromethorphan is an *N*-methyl-D-aspartate (NMDA) receptor antagonist which has been shown to inhibit the development of cutaneous secondary hyperalgesia after tissue trauma. We studied 60 ASA I–II patients undergoing total abdominal hysterectomy in a randomized, double-blind, placebo-controlled study. Patients received either dextromethorphan 27 mg capsules, two doses before operation and three doses in the first 24 h after operation, or placebo. Visual analogue pain scores (VAS) at 24 and 48 h were assessed at rest, on coughing and on sitting up, and were not significantly different between groups. Morphine consumption from a patient-controlled analgesia (PCA) device was also not significantly different between groups. Evidence of secondary hyperalgesia was assessed with von Frey hairs 10 cm above the Pfannenstiel incision. Both groups of patients exhibited evidence of secondary hyperalgesia after 24 and 48 h but there were no significant differences between groups. There was also no difference between groups in VAS scores at 1 month. (*Br. J. Anaesth.* 1998; 81: 731–736).

Keywords: pharmacology, dextromethorphan; pain, post-operative; pain, mechanism.

Secondary hyperalgesia is a pain state which may develop during and after surgery and is manifest clinically as mechanical allodynia, that is the perception of pain in response to normally innocuous mechanical stimuli, in normal tissue surrounding an area of tissue trauma.<sup>1</sup> The development of this pain state has been shown previously to be dependent on activation of the *N*-methyl-D-aspartate (NMDA) receptor located at the dorsal horn of the spinal cord.<sup>2–5</sup> Secondary hyperalgesia has been shown to contribute to generation of pain after tissue injury in animals.<sup>2,6,7</sup> Richmond, Bromley and Woolf<sup>8</sup> have shown, in humans, that postoperative morphine consumption after total abdominal hysterectomy is decreased when an attempt is made to prevent perioperative activation of the NMDA receptor by pre-emptive administration of i.v. morphine.

Dextromethorphan is a weak, non-competitive NMDA antagonist which has been used as an anti-tussive agent for more than 30 yr. It has been shown to inhibit the development of cutaneous secondary hyperalgesia in humans after peripheral burn injury<sup>9,10</sup> and to reduce temporal summation of pain which is an NMDA-dependent event.<sup>11</sup>

The aims of this study were to assess the analgesic benefits of the NMDA antagonist, dextromethorphan, in patients undergoing total abdominal hysterectomy, when the drug was administered in the perioperative period.

### Patients and methods

The study was approved by the Queen's University Research Ethics Committee. Patients presenting for elective total abdominal hysterectomy with or without bilateral salpingo-oophorectomy were recruited after providing written, informed consent, and were allocated randomly (computer-generated list) to either the active or control group. Exclusion criteria for entry to the study included history of a chronic pain syndrome (e.g. fibromyalgia), patients receiving drugs with actions at the spinal cord (e.g. antidepressants), or aspirin within 2 weeks of admission. The consumption of non-steroidal anti-inflammatory drugs (NSAID) other than aspirin was discontinued at least 24 h before operation.

A 100-mm visual analogue score (VAS) for pain was explained to the patients at the preoperative assessment (0 = no pain and 100 = worst imaginable pain). It was explained how their wounds would be assessed after operation with von Frey hairs, which are a series of 20 nylon monofilaments that exert a specific force when bent end on to the patient's skin.

All patients received diazepam 10 mg on the evening before surgery, and diazepam 10 mg, 1–2 h before operation. Patients in the active treatment group also received dextromethorphan 27 mg capsules before operation: one on the night before surgery and one with their premedicant. After operation three further doses were given at 8, 16 and 24 h after operation. Patients in the control group received placebo capsules at the same time intervals. All of the study drugs were prepared by the hospital pharmacy and the study was carried out in a double-blind manner.

On arrival in the operating theatre, an i.v. cannula was inserted into the dorsum of the hand and 1 litre of Hartmann's solution was commenced. Monitors connected before induction of anaesthesia included peripheral oxygen saturation ( $Sp_{O_2}$ ), electrocardiograph (ECG) and arterial pressure (AP) recorded

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Table 1 Patients excluded from the study within the first 24 h

Group	Reason for exclusion
Placebo	Received diclofenac
Placebo	Received diclofenac
Placebo	Returned to operating theatre
Placebo	Returned to operating theatre
Active	Received diclofenac
Active	Received i.m. morphine after operation
Active	Vaginal hysterectomy

Table 2 Patient data (mean (SD or range)). No significant differences

	Dextromethorphan (n=27)	Placebo (n=26)
Age (yr)	45 (30–58)	45 (37–63)
Weight (kg)	65 (11.5)	66 (12.1)
Height (cm)	156 (23.6)	162 (5.0)
Duration of surgery (min)	56 (18.8)	63 (13.7)
Intraoperative morphine (mg)	7 (1.4)	7 (1.4)

non-invasively at 5-min intervals. Each patient was preoxygenated for 2 min with 100% oxygen, after which anaesthesia was induced with propofol 2–3 mg kg<sup>-1</sup>. Tracheal intubation was facilitated with atracurium 0.5 mg kg<sup>-1</sup>. Anaesthesia was maintained with 1–3% isoflurane and 30–40% oxygen in nitrous oxide, and the patients' lungs were ventilated to normocapnia. Ten minutes after a standardized Pfannenstiel incision was made, morphine 0.1–0.15 mg kg<sup>-1</sup> i.v. was given, with further increments administered at the discretion of the attending anaesthetist. Other drugs given during the intraoperative period were: antibiotics (either amoxicillin–clavulonic acid 1.2 g or cefuroxime 1.5 g), ondansetron 4 mg, neostigmine 2.5 mg and glycopyrrolate 0.5 mg.

After tracheal extubation at the end of operation, patients were transferred to the recovery ward where the nursing staff were free to administer bolus doses of morphine 2 mg i.v. every 3 min as required. Patients were assessed by an anaesthetist if they received morphine 10 mg before additional doses were prescribed. I.v. morphine was also available via a patient-controlled analgesia (PCA) system set to deliver 1-mg boluses of morphine with a 5-min lock-out interval. Postoperative nausea and vomiting were treated with prochlorperazine 12.5 mg i.m. 8 h as required. No NSAID was prescribed for the first 48 h after operation.

Patients were assessed after 24 and 48 h by one of the authors. Total postoperative morphine consumption, including that received in the recovery ward, was recorded. VAS pain scores with the patient lying at rest, on coughing (maximal cough after vital capacity inspiratory breath) and on sitting up from the lying position were recorded also.

Touch thresholds were determined at the medial side of the patient's right forearm and 10 cm above the incision, with von Frey hairs. Three points were examined above the wound: one at the midline and one halfway between the midline and the edge of the wound on the left and right sides. Patients were asked to close their eyes and von Frey hair No. 1 was applied to the area to be tested. Each hair was applied once to the site, and the patient was asked to report when they were first aware of the light touch of

the hair, which was recorded as the touch threshold. Pain thresholds were determined at the same sites as the touch thresholds. Patients were asked to open their eyes for this assessment and to report when the sensation elicited by the von Frey hair first became painful. This force was recorded as the pain threshold. The threshold at the wound for touch and pain was subtracted from that at the forearm to yield a "von Frey threshold" for each assessment.<sup>8</sup>

All patients were given a written questionnaire for completion 1 month after operation. They were asked if they still had pain around their wound and if they had, their worst daily VAS pain score. If they had no pain, duration of postoperative wound pain was elicited. They were asked also if they still required analgesics for wound pain, and if so, which analgesics they were taking.

Statistical analysis was carried out using SPSS for Windows Version 7 operated from a 133 MHz IBM compatible PC. Patient data, VAS scores, morphine consumption and von Frey thresholds were analysed with the Mann–Whitney *U* test. Duration of postoperative pain and VAS scores at 1 month were also compared with the Mann–Whitney test. The incidence of side effects was compared using the chi-square test. A significant result was assumed at  $P < 0.05$ .

The study was able to determine, with 90% power at the 5% significance level, a difference of at least 14 mm in VAS scores at rest and on sitting up, at 24 h, and 19 mm on coughing at 24 h. A difference in 24-h morphine consumption of 18 mg between groups could be detected at the same level of power and significance.

## Results

Sixty patients were recruited to the study although seven patients were excluded within the first 24 h (table 1). Data from 53 patients were available for analysis, 27 from the active treatment group and 26 from the placebo group. There were no significant differences between groups for age, weight, height, duration of surgery or intraoperative morphine consumption (table 2).

Total postoperative morphine consumption was similar between groups after 24 h (fig. 1) and there were no significant differences between VAS pain scores at rest, on coughing or on sitting up (fig. 2).

Within the first few weeks of the study commencing, the nurses on the gynaecology ward expressed their concern that patients in the study were being disadvantaged for several reasons. First, they had to continue receiving PCA morphine while those not in the study had their PCA devices removed after 24 h to facilitate mobilization. Second, they were prevented from receiving diclofenac on the second postoperative day, again contrary to standard treatment for this group of patients in this particular hospital.

After hearing these views, we felt that if there was any doubt that these patients were disadvantaged through involvement in the study, that the protocol should be altered. Thus it was decided to omit the 48-h assessment and to prescribe diclofenac after the 24-h assessment, where appropriate. However, assessments at 48 h for 26 patients were obtained before this decision was made.

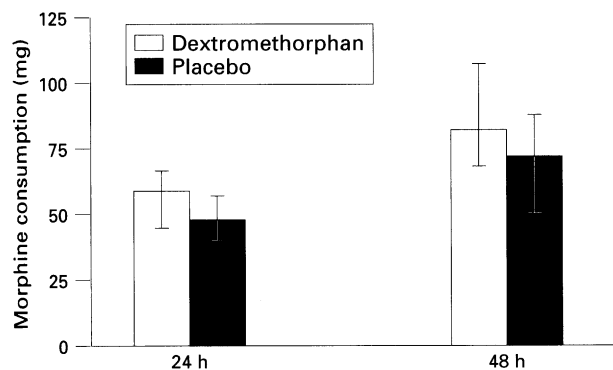


Figure 1 Postoperative morphine consumption (median, interquartile range) at 24 h ( $n=27$  in the dextromethorphan group and  $n=26$  in the placebo group) and at 48 h ( $n=14$  in the dextromethorphan group and  $n=12$  in the placebo group). No significant differences.

The von Frey thresholds between groups for pain were not significantly different, with both showing evidence of mechanical allodynia in the areas tested, while the thresholds for touch were also comparable, with the slightly negative values indicating some decreased sensitivity to light touch in the area of allodynia (table 3). At 48 h, the results from 27 patients were available for analysis, 15 from the active treatment group. However, one patient from the active treatment group was unable to co-operate with VAS measurements because of nausea, although she was able to complete the other parts of the assessment.

Morphine consumption was comparable after 48 h (fig. 1) while there were no significant differences in VAS scores at rest, on coughing or on sitting up (fig. 3). The von Frey thresholds for pain were also comparable between groups, although a significant difference was found in touch thresholds (table 3).

The incidence of side effects, possibly attributable to dextromethorphan, is shown in table 4. Compliance with the study drug regimen was 100%, despite the high incidence of postoperative nausea.

Postoperative questionnaires were returned after 1 month by 39 patients, 19 from the active treatment group. There were no significant differences between pain scores (mm) in the dextromethorphan and placebo groups after 1 month (median 0.0 (interquartile range 0–19) vs 15.5 (0–23),  $P=0.21$ ).

**Discussion**

We have shown that there was no obvious benefit in perioperative administration of dextromethorphan in patients undergoing total abdominal hysterectomy when used within the confines of the chosen anaesthetic regimen, on morphine consumption, early and late postoperative pain or clinical evidence of secondary hyperalgesia.

Table 3 Von Frey thresholds (g) for touch and pain, expressed as median (interquartile range). The threshold for touch in the active treatment group was greater at 48 h

	Dextromethorphan	Placebo	P
24 h	( $n=27$ )	( $n=26$ )	
Touch	0 (-0.89–0.00)	1 (-78–0.00)	0.20
Pain	60 (0.53–81.3)	79 (12.9–152.9)	0.20
48 h	( $n=15$ )	( $n=12$ )	
Touch	0 (0 to -0.01)	-0.7 (-2 to -0.11)	0.04
Pain	13 (0–38)	2 (0–55)	0.58

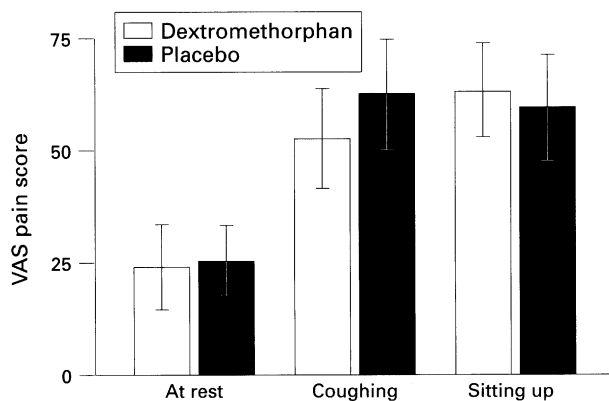


Figure 2 VAS pain scores at 24 h in the dextromethorphan group ( $n=27$ ) and in the placebo group ( $n=26$ ), at rest, on coughing and on sitting up from the lying position (median, interquartile range). No significant differences.

Much work in animals has shown that the receptive fields of dorsal horn neurones expand after peripheral inflammation<sup>6</sup> with an increased state of excitability developing centrally which may persist long after afferent C-fibre activity has ceased.<sup>12,13</sup> Clinically, this is manifest as mechanical allodynia at peripheral sites distant from the inflamed area, and hyperpathia (i.e. increased pain in response to a normally painful stimulus). Our patients, on both the first and second postoperative days, displayed evidence of secondary hyperalgesia with mechanical allodynia 10 cm above the skin incision, as manifest by positive von Frey thresholds. We did not examine evidence of hyperpathia, as this would have involved application of a painful force to the area of allodynia and patients being asked to record the VAS to this force. We felt that patient compliance with this part of the study would have been low in view of the fact that a detailed and time-consuming assessment was already being carried out. However, previous workers have also omitted this assessment in their measurement of secondary hyperalgesia after total abdominal hysterectomy<sup>8,14</sup> and have relied instead on von Frey pain thresholds to assess methods of inhibiting dorsal horn changes.

Dextromethorphan is a water-soluble agent with weak, non-competitive NMDA blocking properties.<sup>15,16</sup> It is metabolized by O-dealkylation to yield the active metabolite dextrorphan, which is a more potent antagonist at the NMDA receptor.<sup>16,17</sup> The efficacy of the NMDA-blocking properties of

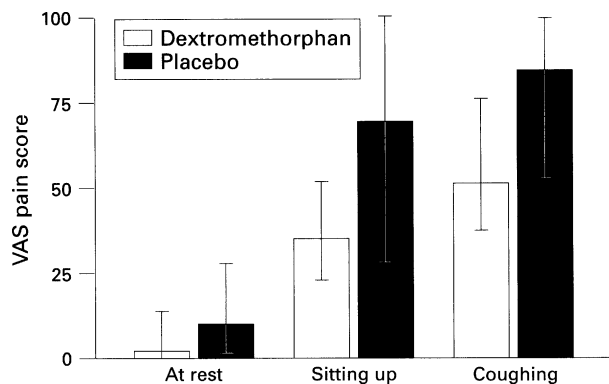


Figure 3 VAS pain scores at 48 h in the dextromethorphan and placebo groups, at rest, on coughing and on sitting up from the lying position (median, interquartile range). No significant differences.

Table 4 Incidence of side effects attributable to dextromethorphan after 24 and 48 h (number of patients affected (%)). No significant differences

	Dextromethorphan	Placebo
0–24 h	(n=27)	(n=26)
Dizziness	12 (44)	11 (42)
Hot flushes	7 (26)	4 (15)
Tremor	5 (19)	6 (23)
Constipation	20 (74)	24 (92)
Drowsiness	24 (89)	26 (100)
Heartburn	6 (22)	26 (100)
Nausea	19 (70)	19 (73)
Vomiting	8 (30)	14 (54)
24–48 h	(n=14)	(n=12)
Dizziness	6 (43)	5 (42)
Hot flushes	4 (29)	5 (38)
Tremor	0 (0)	6 (50)
Constipation	11 (79)	5 (42)
Heartburn	5 (36)	3 (25)
Nausea	5 (36)	3 (25)
Vomiting	2 (14)	1 (8)

dextromethorphan have been shown in several animal studies, where it afforded neuronal protection in an ischaemic brain model,<sup>18,19</sup> inhibited the development of tolerance to morphine<sup>20,21</sup> and was neuroprotective in glutamate-induced neuronal injury.<sup>22</sup> Electrophysiological work has also shown that dextromethorphan produced a reduction in wind-up after repetitive C-fibre stimulation.<sup>23</sup> In human studies, it has also been shown to reduce the clinical evidence of secondary hyperalgesia after thermal injury.<sup>9,11</sup> The active metabolite of dextromethorphan, dextrorphan, has also been shown to be beneficial in animal models where antagonism of the NMDA receptor is the desired outcome, for example in studies of neuropathic pain.<sup>10,24</sup>

Although the above studies provide clinical evidence that dextromethorphan exhibits NMDA-blocking properties, the exact site of action remains unresolved. It seems to possess both presynaptic actions, where it inhibits the release of glutamate at the dorsal horn,<sup>25</sup> together with postsynaptic actions. However, its site of postsynaptic action is not certain as it possesses relatively low affinity for phencyclidine binding sites and has little affinity for MK-801 or glycine recognition sites. Thus indirect modulation of the NMDA receptor may be the mechanism by which its postsynaptic actions are mediated.<sup>22</sup> In contrast, dextrorphan exerts its effects via binding to the phencyclidine site on the NMDA receptor complex.

Work has also been carried out which has produced negative results. Kauppila, Gronroos and Pertovaara,<sup>26</sup> in a study in volunteers, found that dextromethorphan 100 mg orally did not alter visual analogue pain scores after experimental limb ischaemia or topical capsaicin injection. When a dose of 200 mg was given, the incidence of side effects was 100% with withdrawal of 50% of the volunteers from the study. McQuay and colleagues<sup>27</sup> investigated dextromethorphan in patients with neuropathic pain at doses of 40.5 mg and 81 mg daily. No significant analgesic benefit was shown, while seven of 19 patients in the study withdrew because of adverse effects.

Dextromethorphan has been available as an anti-tussive agent for more than 30 yr and has a strong safety profile with few severe drug reactions.<sup>28–30</sup>

However, troublesome side effects occur as the dose is increased.<sup>27,31</sup> McQuay and colleagues<sup>27</sup> found that significant side effects were produced with 81 mg daily in patients with neuropathic pain, but the optimum dose for NMDA antagonism in the perioperative period has not been determined. Hollander and colleagues<sup>31</sup> have used up to 10 mg kg<sup>-1</sup> day<sup>-1</sup> for patients with amyotrophic lateral sclerosis, while Albers and colleagues<sup>28</sup> found that 60 mg qid was free from side effects in patients at risk of brain ischaemia. In their study on human volunteers, Price and colleagues<sup>11</sup> found that oral doses of 30 mg and 45 mg were effective at reducing the temporal summation of second pain after peripheral thermal injury. The optimum dose of dextromethorphan in the perioperative period is not known, although it is probable that the doses used in this study were too small, as the incidence of adverse effects attributable to dextromethorphan was not significantly different between the two groups. A dose-finding study for dextromethorphan in the perioperative period would enable the maximum acceptable dose to be assessed after surgery. Coderre and Van Empel<sup>32,33</sup> have shown that the antinociceptive effects of NMDA antagonists in persistent nociceptive models (formalin test) were apparent only at doses which produced significant adverse side effects. The antinociceptive effects were reported to be far from maximal despite significant side effects of both competitive and non-competitive NMDA antagonists administered intrathecally. If the same situation applies to humans in the perioperative period, then few NMDA antagonists would be suitable for use in this period because of the poor adverse effect profile at higher doses.

Another interpretation of our results is that NMDA receptor antagonism did occur, but that this was not detectable using mechanical allodynia, and that thermal allodynia should have been examined also. This is supported by evidence from animal studies which has shown that NMDA receptor activation alone generates thermal allodynia and hyperalgesia, while mechanical allodynia and hyperalgesia require activation of AMPA and metabotropic glutamate receptors, the effects of which are enhanced by NMDA receptor activation.<sup>34</sup> However, many previous studies in animals have shown that NMDA receptor activation after peripheral inflammation leads to generation of mechanical allodynia and the intensity of this is diminished when efforts are made to inhibit activation of the NMDA receptor.<sup>3–6,35,36</sup> More recent work, however, has shown that postoperative pain behaviour in a rat model is not improved by administration of an NMDA antagonist intrathecally.<sup>37</sup>

The intraoperative analgesic regimen in theatre involved administration of i.v. morphine 10 min after skin incision. Although this differs from our normal practice, when an opioid is given at induction of anaesthesia before skin incision, we felt that our patients would not be disadvantaged by this study regimen. Previous studies have shown that pre-incisional morphine in this group of patients prevents the development of secondary hyperalgesia in the first 24 h after operation<sup>8,14</sup> and that there is significant evidence of secondary hyperalgesia if morphine administration is left until closure of the peritoneum.<sup>8</sup> Completely obtunding the development of secondary

hyperalgesia by giving morphine at induction of anaesthesia would have resulted in the need for large numbers of patients in our study to show a difference between active and placebo groups. Alternatively, leaving morphine administration until the end of operation may have exposed our patients to unnecessary morbidity. It was decided that administration 10 min after skin incision was a reasonable compromise, as preclinical studies suggest that opioids delivered before the end of surgery may have a beneficial effect on the dorsal horn.<sup>38</sup> However, as our results have shown, this resulted in clinical evidence of NMDA receptor activation, although we cannot say how this would compare with groups given morphine before incision or on peritoneal closure. Further work on the optimum timing of administration of intraoperative opioids is required.

It is interesting that the combined use of an agent with presynaptic actions at the dorsal horn (i.e. morphine), together with an agent with postsynaptic actions (i.e. dextromethorphan), did not prevent the development of secondary hyperalgesia, as the combination of these groups of agents produces synergistic effects at the dorsal horn.<sup>39</sup>

In summary, we have shown that the perioperative use of the NMDA antagonist, dextromethorphan, did not offer any benefit to patients undergoing abdominal hysterectomy within the confines of the study methodology.

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