Effect of systemic N-methyl-D-aspartate receptor antagonist (dextromethorphan) on primary and secondary hyperalgesia in humans

S. ILKJÆR, J. DIRKS, J. BRENNUM, M. WERNBERG AND J. B. DAHL

Summary

Dextromethorphan is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist known to inhibit wind-up and central hyperexcitability of dorsal horn neurones. We studied 24 healthy, unmedicated male volunteers, aged 21–28 yr, in a randomized, double-blind, placebo-controlled, crossover study. Burn injuries were produced on the medial surface of the dominant calf with a 25 × 50 mm rectangular thermode. On three separate days, at least 1 week apart, subjects were given oral dextromethorphan 60 mg, 120 mg or placebo. Dextromethorphan reduced the magnitude of secondary hyperalgesia to pinprick but not to stroke. Dextromethorphan had no influence on primary hyperalgesia, pain during prolonged noxious heat stimulation or heat pain detection thresholds in undamaged skin. Side effects were frequent but clinically acceptable. The effects of dextromethorphan were in agreement with experimental studies indicating that dextromethorphan is a NMDA receptor antagonist. The effects of dextromethorphan in the burn injury model were similar to those of ketamine and distinct from those of local anaesthetics and opioids. (Br. J. Anaesth. 1997; 79: 600–605).

Key words


Over the past several years, evidence has accumulated that peripheral tissue injury may lead to hyperexcitability of wide dynamic range (WDR) neurones in the dorsal horn. Prolonged C-afferent activity evokes wind-up, a state that results in increased receptive fields and exaggerated responses of the WDR neurones to afferent input. Wind-up can augment responses of dorsal horn neurones up to 20-fold in magnitude and duration. This state of hyperexcitability may even continue after cessation of the peripheral input. Central sensitization induces altered processing of afferent activity evoked by both innocuous and noxious stimuli. Clinically this is manifested as allodynia (pain caused by a stimulus that does not normally provoke pain) and hyperalgesia (increased response to a stimulus that is normally painful). Injury-induced sensitization of dorsal horn neurones has been implicated as an important contributor to both acute and chronic pain states. Experimental studies have indicated that the N-methyl-D-aspartate (NMDA) receptor plays a significant role in wind-up and spinal hyperexcitability. Both animal and human studies have shown that NMDA antagonists can reduce spinal hyperexcitability, leading to renewed interest in NMDA receptor antagonists such as ketamine and dextromethorphan.

Dextromethorphan has been used as an antitussive agent for more than 30 yr. Since its development, little attention has been directed towards the CNS pharmacology of this drug. The discovery of high affinity binding sites for dextromethorphan in the brain and possible anticonvulsant, neuroprotectant, anti-ischaemic and anti-pain properties has lead to an increased interest in the drug. Both dextromethorphan and its metabolite dextrorphan appear to be NMDA receptor antagonists. Experimental studies indicated that dextromethorphan reduced NMDA-mediated nociceptive responses in the dorsal horn neurones and a reduction in wind-up has been indicated in a clinical study. It has been reported that the side effects of dextromethorphan are rare and mostly unimportant, and that the drug has a wide margin of safety.

Cutaneous heat injury evokes allodynia and hyperalgesia for mechanical and heat stimuli within the injured area (primary hyperalgesia) and allodynia for mechanical, but not heat, stimuli in an area surrounding the injury (secondary hyperalgesia). There is convincing evidence that secondary hyperalgesia is a result of altered central processing of afferent activity because of sensitization of dorsal horn neurones, whereas primary hyperalgesia seems to be caused by a combination of sensitization of...
The burn injury model has been used previously to study the effects of various analgesics in human volunteers. The aim of the study was to investigate the effects of oral dextromethorphan on pain and hyperalgesia after a burn injury in human volunteers.

**Subjects and methods**

We studied 25 healthy, unmedicated male volunteers, mean age 24 (21–28 yr), after obtaining informed consent and approval from the regional Ethics Committee and the Danish National Health Board. One subject was excluded because of incorrect medication on one examination day. The study was performed in a quiet room with subjects in a semi-supine position. Each subject had been familiarized with the burn injury and measurement procedures on a separate day.

**HYPERALGESIA**

Burn injuries were produced on the medial surface of the dominant calf (L3–4 dermatome) with a 25 × 50 mm rectangular thermode (Thermostat, Somedic A/B Sweden) applied to the skin with a standardized pressure (8 kPa). The temperature of the thermode was 47°C and application time was 7 min. This resulted in a first-degree burn injury, that is redness without blistering.

Pain ratings were performed continuously by the volunteer by moving a lever that controlled a vertical bar on a computer screen (sample rate 2 Hz). The visual analogue score (VAS) was anchored with the descriptors “no pain” (numerical value = 0) and “worst possible pain” (numerical value = 100). The interpretation of “pain” was left to the subject, who was instructed to apply the same interpretation throughout the study.

Brief conditioning was produced with the same thermode placed on the centre of the anterior side of the thigh at 45°C. After 3 min of heating, the border of hyperalgesia to pinprick and stroke stimuli was determined along four linear paths arranged radially around the thermal injury (see below). Immediately after these determinations the thermode was removed. These brief conditioning stimuli induced slight or no pain during heating and no spontaneous sensations after termination. The mechanical hyperalgesia induced by these brief conditioning stimuli never lasted more than a few minutes beyond the duration of the conditioning stimuli.

**MEASUREMENT OF MECHANICAL HYPERALGESIA**

The temperature of the injured site was stabilized at 35°C, with the above described thermode, from 1 min before and throughout assessment of mechanical hyperalgesia. The border of hyperalgesia to pinprick and stroke stimuli was determined by stimulating along four linear paths arranged radially around the thermal injury in steps of 5 mm at intervals of 1 s, starting well outside the hyperalgesic area where neither stimulus type evoked pain. Stimulation continued towards the injury until subjects reported a clear change in sensations (“burning”, “tenderness”, “more intense pricking”). The areas of hyperalgesia were calculated using a vector algorithm. Pinprick was performed with the von Frey technique using a nylon filament with a diameter of 1 mm and a bending force of 1.15 N. Stroke stimulation was performed by lightly stroking the skin with a gauze swab.

**Table 1** Experimental design

<table>
<thead>
<tr>
<th>Time</th>
<th>Actions/measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baselines</td>
<td>Area of secondary hyperalgesia to pinprick and stroke during brief conditioning, thigh.</td>
</tr>
<tr>
<td>0 min</td>
<td>Heat pain detection threshold (HPDT), right and left calf</td>
</tr>
<tr>
<td>105–115 min</td>
<td>Oral dextromethorphan 60 mg, 120 mg or placebo</td>
</tr>
<tr>
<td>120–127 min</td>
<td>Area of secondary hyperalgesia to pinprick and stroke during brief conditioning, thigh</td>
</tr>
<tr>
<td>180–200 min</td>
<td>HPDT, right and left calf</td>
</tr>
<tr>
<td>240–260 min</td>
<td>Area of secondary hyperalgesia to pinprick and stroke around burn injury, right calf</td>
</tr>
<tr>
<td>240–260 min</td>
<td>Area of secondary hyperalgesia to pin prick and stroke around burn injury, right calf</td>
</tr>
</tbody>
</table>

**MEASUREMENT OF THERMAL THRESHOLDS**

Heat pain detection threshold (HPDT) was defined as the lowest temperature perceived as painful. The thermode was identical to that used for production of the burn injury. HPDT was determined from a baseline temperature of 32°C with a rate of change of 1°C s⁻¹. By pressing a button, subjects indicated when the pertinent threshold was reached. This value was recorded and the stimulator returned to baseline. If the cut-off limit (52°C) was reached before the pertinent threshold, the thermode returned automatically to baseline and a threshold of 52°C was registered (it did not happen in any of the threshold measurements). Each threshold was calculated as the average of three measurements with randomized intervals (6–10 s) between each stimulation. Thermal thresholds were determined at the site of injury and at the corresponding site of the contralateral, unburned calf.
ASSESSMENT OF SIDE EFFECTS

Drowsiness was assessed on an 11-point analogue scale (0=completely awake; 10=almost asleep). Discomfort was assessed on an 11-point analogue scale (0=no discomfort; 10=maximum discomfort). Dizziness was assessed on an 11-point analogue scale (0=no dizziness, 10=maximum dizziness). Nausea was registered as four graduations (none, light, moderate or severe). Finally, subjects were asked if they experienced other sensations.

EXPERIMENTAL PROCEDURE

On three separate days, at least 1 week apart, subjects received oral dextromethorphan 60 mg, 120 mg or placebo, 2 h before induction of hyperalgesia. The study was double-blind and the order of treatments was randomized. Timing of the various assessments is shown in table 1.

STATISTICAL ANALYSIS

Data are presented as median (lower and upper quartiles). Variables were evaluated with Wilcoxon’s test for paired data. All significant P values were corrected with Bonferroni’s test for repeated measurements. P<0.05 was considered statistically significant.

Results

CONTROL (PLACEBO) DAY

Pain during burn injury increased rapidly during the first 15–30 s, reached a plateau and then remained relatively stable during the remaining 6 min (fig. 1). After induction of injury, no spontaneous pain or other sensations were experienced from the site of injury.

The borders of secondary hyperalgesia for pinprick and stroke stimuli surrounding the burn injury on the calf (table 2) and the area of secondary hyperalgesia for pinprick and stroke stimuli evoked by brief conditioning on the thigh (table 3) were detected easily in all subjects.

HPDT inside the burned area decreased from a baseline value of 47.6 (47.0–48.8) °C to 44.4 (43.6–45.8) °C, 60 min after the injury, and remained decreased throughout the study (P<0.05) (table 4). HPDT on the contralateral calf did not change throughout the study (P>0.05) (table 4).

EFFECTS OF DEXTROMETHORPHAN

There were no differences in pain ratings during

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**Table 2** Area of secondary hyperalgesia to pinprick and stroke stimuli (cm²) around the burn injury during treatment with dextromethorphan 120 mg, 60 mg and placebo (medians (lower and upper quartiles)). *P<0.05 compared with placebo

<table>
<thead>
<tr>
<th></th>
<th>Dextromethorphan 120 mg</th>
<th>Dextromethorphan 60 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pinprick</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>180 min</td>
<td>69 (43–82)*</td>
<td>67 (52–94)</td>
<td>78 (54–110)</td>
</tr>
<tr>
<td>240 min</td>
<td>60 (49–84)</td>
<td>65 (43–110)</td>
<td>75 (54–104)</td>
</tr>
<tr>
<td>Stroke stimuli</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>180 min</td>
<td>34 (21–55)</td>
<td>37 (27–48)</td>
<td>41 (25–77)</td>
</tr>
<tr>
<td>240 min</td>
<td>35 (19–56)</td>
<td>38 (24–57)</td>
<td>35 (21–59)</td>
</tr>
</tbody>
</table>

**Table 3** Area of secondary hyperalgesia to pinprick and stroke stimuli induced by brief conditioning on the thigh during treatment with dextromethorphan 120 mg, 60 mg and placebo (medians (lower and upper quartiles)). *P<0.05 compared with placebo

<table>
<thead>
<tr>
<th></th>
<th>Dextromethorphan 120 mg</th>
<th>Dextromethorphan 60 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pinprick</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>97 (72–120)</td>
<td>89 (71–115)</td>
<td>109 (81–129)</td>
</tr>
<tr>
<td>105 min</td>
<td>93 (59–116)</td>
<td>93 (60–140)</td>
<td>96 (67–122)</td>
</tr>
<tr>
<td>180 min</td>
<td>71 (42–116)*</td>
<td>86 (57–133)</td>
<td>99 (70–117)</td>
</tr>
<tr>
<td>240 min</td>
<td>81 (46–115)</td>
<td>110 (64–141)</td>
<td>89 (73–131)</td>
</tr>
<tr>
<td>Stroke stimuli</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>54 (38–74)</td>
<td>63 (45–93)</td>
<td>52 (34–84)</td>
</tr>
<tr>
<td>105 min</td>
<td>50 (26–87)</td>
<td>67 (40–103)</td>
<td>52 (35–83)</td>
</tr>
<tr>
<td>180 min</td>
<td>47 (35–55)</td>
<td>57 (47–90)</td>
<td>59 (37–73)</td>
</tr>
<tr>
<td>240 min</td>
<td>47 (38–65)</td>
<td>67 (50–104)</td>
<td>59 (38–89)</td>
</tr>
</tbody>
</table>

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**Figure 1** Median pain scores (VAS) during burn injury after treatment with dextromethorphan 120 mg (---), 60 mg (....) and placebo (----) (ns, Wilcoxon rank test).
induction of the burn injury between dextromethorphan 120 mg, 60 mg or placebo (fig. 1) (120 mg vs placebo, \( P=0.60 \); 60 mg vs placebo, \( P=0.98 \) (Wilcoxon rank test)).

**MEASUREMENT OF MECHANICAL HYPERALGESIA**

At the burn injury (calf) the areas of secondary hyperalgesia to pinprick but not to stroke were reduced by dextromethorphan 120 mg compared with placebo at 180 min after administration of the drug (\( P<0.008 \), corrected for multiple comparisons (pinprick), \( P=0.07 \) (stroke)). There was no difference in the areas at 240 min (\( P=0.10 \) (pinprick), \( P=0.74 \) (stroke)) (table 2).

Dextromethorphan 60 mg had no influence on the area of secondary hyperalgesia for pinprick (\( P=0.24 \), \( P=0.51 \)) or for stroke (\( P=0.29 \), \( P=0.08 \)) at 180 min or 240 min after administration of the drug, respectively (table 2).

On the thigh, the area of secondary hyperalgesia to pinprick but not to stroke was reduced by dextromethorphan 120 mg compared with placebo at 180 min but not at 240 min after drug administration (\( P=0.048 \), corrected for multiple comparisons). No significant effects were observed with dextromethorphan 60 mg (table 3).

**MEASUREMENT OF THERMAL THRESHOLDS**

At the site of injury there was no difference in the decrease in HPDT between dextromethorphan 120 mg, dextromethorphan 60 mg or placebo treatment (dextromethorphan 120 mg vs placebo, \( P>0.1 \); dextromethorphan 60 mg vs placebo, \( P>0.2 \)). Hence, dextromethorphan in these doses did not influence primary hyperalgesia (table 4).

At the contralateral uninjured calf there was no difference in HPDT between dextromethorphan 120 mg, dextromethorphan 60 mg or placebo treatment (dextromethorphan 120 mg vs placebo, \( P>0.07 \); dextromethorphan 60 mg vs placebo, \( P>0.1 \)). Hence dextromethorphan had no influence on HPDT in non-injured skin (table 4).

**SIDE EFFECTS**

Dizziness was more pronounced with dextromethorphan 120 mg, but not with 60 mg, compared with placebo (\( P<0.05 \) (range 1–5 on the analogue scale). The difference was significant at 105 and 180 min, but not at 240 min after administration. Only a few subjects experienced slight nausea, drowsiness and discomfort, but these adverse effects were observed also in the placebo group. In general, the frequency of side effects was low, and after 240 min they had almost disappeared. No volunteer wished to leave or was excluded from the study because of side effects. All volunteers were able to collaborate fully during the various assessments without problems.

**Discussion**

In this study we found dextromethorphan to have a slight but statistically significant inhibitory effect on mechanical allodynia for pinprick in the area of secondary hyperalgesia after a burn injury in humans. There was no effect on heat pain detection thresholds in normal or injured skin, on mechanical alldynia for stroke in the area of secondary hyperalgesia or on pain evoked by prolonged heat stimuli.

NMDA receptor antagonists differ from "classic" analgesics in their mechanisms of action. They have no effect on the initial nociceptive input, as do opioids or local anaesthetics, but they reduce wind-up and injury-induced facilitation of nociceptive neurones in the CNS. Thus these drugs are expected to exert their analgesic effects only under conditions where tissue damage (e.g. burn injury) or repetitive C-fibre stimulation has induced hyperexcitability of dorsal horn neurones.

Experimental studies have shown that dextromethorphan can reduce wind-up,\(^3\) formalin-induced increases in spinal cord c-fos mRNA\(^5\) and pain behaviour.\(^4\) Furthermore, dextromethorphan attenuates analgesic tolerance to morphine,\(^25\) and it possesses additive analgesic effects when combined with NSAID.\(^27\)

Human studies on dextromethorphan and pain have shown controversial results.\(^10\) Human studies on dextromethorphan and pain have shown controversial results.\(^10\) In a double-blind, randomized, placebo-controlled crossover design where six volunteers were given oral doses of dextromethorphan 15, 30 or 45 mg, or placebo, Price and colleagues found that dextromethorphan reduced slow temporal summation of electrically and thermally evoked second pain (a correlate with wind-up) in a dose-dependent manner.\(^10\) In another study, oral dextromethorphan 100 and 200 mg did not attenuate pain produced by

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**Table 4** Heat pain detection thresholds (ºC) on the unburned and burned calf during treatment with dextromethorphan 120 mg, 60 mg and placebo (medians (lower and upper quartiles))

<table>
<thead>
<tr>
<th></th>
<th>Dextromethorphan 120 mg</th>
<th>Dextromethorphan 60 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unburned calf</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>48.1 (46.7–49.5)</td>
<td>47.7 (46.6–49.2)</td>
<td>47.8 (46.6–48.9)</td>
</tr>
<tr>
<td>105 min</td>
<td>48.1 (47.3–48.9)</td>
<td>47.4 (46.4–48.2)</td>
<td>47.6 (46.5–48.4)</td>
</tr>
<tr>
<td>180 min</td>
<td>47.6 (46.3–48.2)</td>
<td>47.8 (46.5–48.8)</td>
<td>47.1 (46.2–47.9)</td>
</tr>
<tr>
<td>240 min</td>
<td>47.7 (46.7–49.1)</td>
<td>47.6 (46.5–49.0)</td>
<td>47.7 (46.8–48.4)</td>
</tr>
<tr>
<td><strong>Burned calf</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>48.4 (47.1–50.1)</td>
<td>47.5 (46.5–49.1)</td>
<td>47.6 (47.0–48.8)</td>
</tr>
<tr>
<td>105 min</td>
<td>48.4 (47.3–49.4)</td>
<td>47.3 (46.2–48.7)</td>
<td>47.7 (46.8–48.9)</td>
</tr>
<tr>
<td>180 min</td>
<td>45.6 (43.1–47.1)</td>
<td>45.3 (42.3–47.0)</td>
<td>44.4 (43.6–45.8)</td>
</tr>
<tr>
<td>240 min</td>
<td>46.3 (43.5–47.5)</td>
<td>46.1 (44.0–47.0)</td>
<td>45.5 (44.5–47.5)</td>
</tr>
</tbody>
</table>

Note: \( P\) values are for comparisons between treatments (dextromethorphan 120 mg, 60 mg or placebo) vs placebo, except as noted.

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topical capsaicin or ischaemia 45 min after oral administration, but side effects were pronounced with the higher dose.30 Wind-up, hyperalgesia or other correlates with central neuronal alterations were not evaluated specifically.30 Thus it is uncertain if central hyperexcitability had been induced or if effective plasma concentrations were achieved at the time of assessment.30 One preliminary clinical study has evaluated the analgesic effect of dextromethorphan after oral surgery. Doses of 60 and 120 mg were given before and every 6 h after operation, and pain was evaluated for 48 h after surgery. Dextromethorphan produced a weak analgesic effect 6 h after operation.28 Furthermore, in a double-blind, randomized, crossover study, small doses of dextromethorphan (13.5 and 27 mg three times a day) had no effect on neuropathic pain.20

Dextromethorphan 60 or 90 mg qid or up to 10 mg kg−1 day−1, with total doses in the range 4.8–10 mg kg−1 day−1, respectively, have been administered to patients with either a history of transient ischaemic attacks or with amyotrophic lateral sclerosis, with minor but dose-limiting side effects.31 32 In this study doses of oral dextromethorphan 60 and 120 mg were chosen because of the lack of analgesic effect with smaller doses in a previous clinical study,29 the relatively minor side effects observed with higher doses in neurological patients31 32 and the unacceptable side effects observed with 200 mg in a study in human volunteers.30 The burn injury was induced 2 h after administration of dextromethorphan as plasma concentrations have been found to be at their maximum 2 h (range 1–4 h) after oral intake.32 Dextromethorphan reduced secondary hyperalgesia surrounding a first-degree burn injury, and secondary hyperalgesia during short lasting thermal conditioning of the skin. These findings, together with the lack of effect on heat pain detection thresholds in unburned skin, are consistent with previous experimental results115 and with the observations of Price and colleagues.10 They confirmed that dextromethorphan may reduce injury-induced alterations in dorsal horn neurones without any effect on nociceptive input per se. The reduction was significant for pinprick but not for stroke hyperalgesia 3 h after administration of the drug. Taking the side effects into account this could be the period with the highest plasma concentration of the drug; 4 h after drug administration, side effects were reduced and the reduction in secondary hyperalgesia compared with placebo had disappeared.

Cervero and colleagues examined the appearance of secondary hyperalgesia to pinprick and stroke after non-painful heat stimuli.33 They found that the area of pinprick developed first, followed by flare and hyperalgesia for stroke. This indicates that hyperalgesia to pinprick and stroke may be mediated by different mechanisms.33 In a recent study, ketamine reduced hyperalgesia for both pinprick and stroke because of a burn injury,9 while in another study capsaicin-induced hyperalgesia for pinprick, but not for stroke, was reduced by ketamine.11 This indicates that secondary hyperalgesia for punctuate stimuli are attenuated more by NMDA antagonists than secondary hyperalgesia for stroke. Pain during induction of the burn injury, and heat pain detection thresholds in burned skin, were not influenced by dextromethorphan in contrast with the findings for ketamine.9 One explanation for this discrepancy could be that in our study dextromethorphan had not reached an adequate plasma concentration during induction of the burn injury but may also reveal differences in potency or mechanisms of action between the two drugs.

Although dextromethorphan induced (insignificant) drowsiness at both doses, heat pain detection thresholds in both healthy and injured skin were unaffected by dextromethorphan. This indicates that the reduction in secondary hyperalgesia with dextromethorphan 120 mg was not caused by side effects. Our study is in accordance with previous findings and confirms that dextromethorphan may reduce injury-induced alterations in dorsal horn neurones without any effect on nociceptive input per se. In experimental studies the combination of NSAID and dextromethorphan was found to have additive analgesic effects and the combination with morphine reduced the development of tolerance.25 27 Human studies have not yet been performed. Our study provides a rationale for further studies of the effects of dextromethorphan in combination with other analgesics on clinical pain states, such as postoperative pain.

Acknowledgements

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References


