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# **EFFECTS OF MORPHINE ON THE EXPERIMENTAL ILLUSION OF PAIN PRODUCED BY A THERMAL GRILL**

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## **ABSTRACT**

We compared the effects of systemic morphine on normal (heat and cold) pain and paradoxical burning pain evoked by the simultaneous application of innocuous warm and cold stimuli to the skin.

Twelve healthy volunteers participated in a randomised, double-blind, cross-over study to compare the effects of intravenous administration of morphine (0.025 or 0.1 mg/kg) or placebo (saline). Stimuli were applied to the palm of the right hand with a thermode ("thermal grill") composed of six bars, whose temperatures was controlled by Peltier elements. For each session, we measured the heat and cold pain thresholds and then successively measured the intensity of: i) paradoxical pain evoked by a combination of non noxious warm and cold stimuli; ii) "normal" pain evoked by suprathreshold heat or cold stimuli; iii) non-painful sensations evoked by warm or cold stimuli at temperatures used to produce paradoxical pain. Measurements were performed before, 20 minutes after the administration of morphine or placebo and 5 minutes after the administration of the morphine antagonist, naloxone.

The administration of 0.1 mg/kg of morphine, but not 0.025 mg/kg, induced a significant and naloxone-reversible reduction of paradoxical pain intensity, which was directly correlated with the reduction of normal cold pain. No differences were observed for non-painful thermal sensations.

The paradoxical burning pain evoked by a thermal grill can be modified pharmacologically by analgesics and share some mechanisms with normal pain. This unique experimental 'illusion of pain' may represent a new model to test analgesics in healthy volunteers.

## 1- INTRODUCTION

The paradoxical burning pain induced by the simultaneous application of innocuous warm and cool stimuli to the skin is a unique experimental phenomenon, creating an illusion of pain. This phenomenon, also called the "thermal grill illusion of pain" (TGIP), was described more than a century ago by Thunberg<sup>29</sup> and characterised during the first part of the XXth century<sup>3</sup>. It has been reinvestigated recently using modern techniques because of its potential value for studying pain mechanisms and the interactions between nociceptive and thermal sensory systems<sup>4,8,11,17,19,22,25</sup>. Painful sensation evoked by normally non-painful stimuli is reminiscent of thermal allodynia often observed in pathological conditions; thus, the investigation of TGIP may also have clinical implications.

Recent studies demonstrated that stimulation with a thermal grill, with temperatures well below the heat and cold pain thresholds, is capable of producing a painful burning sensation in a large proportion of healthy volunteers<sup>4,8,22,25</sup>, although a subpopulation (25-30%) of subjects are less responsive<sup>4,22</sup>. Additionally, the occurrence and intensity of paradoxical pain was directly related to the magnitude of the difference in temperature between the warm and cold bars of the grill<sup>4</sup>.

The neurophysiological basis of this paradoxical pain remains unclear. Consistent with the thermosensory disinhibition theory of pain<sup>12,13</sup>, TGIP may result from a reduced level of inhibition of the nociceptive systems normally exerted by cold afferents. Alternatively, it may depend on the convergence and addition of the activity of adjacent cold and warm afferents on CNS multireceptive neurones<sup>4,19</sup>.

We recently demonstrated for the first time that the thermal grill paradoxical pain could be modified pharmacologically<sup>22</sup>. We showed that intravenous injection of a low (sub-anaesthetic) dose of ketamine selectively reduced the intensity of the

paradoxical pain, without affecting normal thermal (heat and cold) painful or non-painful sensations. By contrast, injection of the opioid receptor antagonist naloxone did not affect either the paradoxical or normal pain. Thus, the thermal grill paradoxical pain involves the glutamatergic systems, acting through the N-methyl-D-aspartate (NMDA) receptors, but not the tonic endogenous opioid systems. Moreover, the marked selectivity of ketamine action suggests that some of the mechanisms involved in TGIP are similar to those involved in pathological pain (inflammatory or neuropathic), in particular, hyperalgesia/allodynia phenomena which respond preferentially to NMDA antagonists<sup>7,16,18,20</sup>.

Here, we further investigated the neuropharmacological mechanisms involved in TGIP which could represent a new experimental model for testing analgesics. We analysed the effects of intravenous administration of morphine, on normal (physiological) and paradoxical pain evoked by a thermal grill in healthy volunteers in a randomised, double-blind, placebo-controlled, cross-over study.

## 2- METHODS

This study was performed in a group of paid healthy volunteers following approval by the Ambroise Paré hospital Ethics Committee. Participants were fully informed about the experimental procedures and gave written consent.

### *2.1 Equipment*

Thermal stimuli were produced using a thermode designed and built by SEICER (Mouy, France)<sup>4,22</sup>. The thermode was composed of six bars (1.2 x 16 cm) covered with a copper plate, spaced 2 mm apart for thermal isolation; temperature was controlled by thermoelectric Peltier elements (three per bar). The temperatures of alternate (even- and odd-numbered) bars were controlled independently between 5 and 50 °C to generate various combinations of temperatures (i.e. patterns of the 'thermal grill'). Thermistors placed in each bar provided continuous feedback of the thermode–skin interface temperature (resolution  $\pm 0.3$  °C).

### *2.2 Study design*

The study design was a randomised, double-blind, placebo controlled, cross-over trial. Each volunteer participated in three experimental sessions separated by one week. During each session, volunteers randomly received an intravenous (iv) injection of one of the three treatment: 0.025 mg/kg or 0.1 mg/kg of morphine or placebo (saline). The volume and infusion rate for the placebo was similar to those used for the active drug. Infusions were prepared by a nurse who was not otherwise involved in the experiment. Paradoxical pain was measured five minutes after the non-blinded iv administration of naloxone (0.4 mg).

### *2.3 Experimental procedure*

All experiments were performed at room temperature (21°C) and thermal stimuli were applied to the palm of the right hand. The volunteers were asked to put their hand on the grill, perpendicular to the long axis of the bars, for 30 seconds.

For each experimental session, we recorded the following variables before (control period) and 20 minutes after the end of administration of morphine (0.025 or 0.1 mg/kg) or placebo (saline):

i) The cold pain threshold and the heat pain threshold, using a staircase algorithm. Even-numbered bars were kept at a neutral temperature while the temperature of the odd-numbered bars was changed randomly (either increased or decreased) by steps of 3 to 0.5°C. Subjects had to report whether they perceived each stimulus as painful or not. Temperatures were changed by 3°C following negative responses and by 0.5°C following the first painful stimulus; successive stimuli were changed (increased or decreased) by 0.5°C until the first non-painful sensation was reported.

ii) The combination of thermal stimuli producing paradoxical pain. Paradoxical painful sensation was defined as a painful sensation evoked by a combination of warm and cool stimuli at 4°C above cold pain threshold or 4°C below heat pain threshold, respectively. These parameters were based on our previous study<sup>4</sup>. Then, the mean intensity of paradoxical pain determined at two separate time intervals, 3 minutes apart, were taken as baseline control values. Volunteers were asked to describe the quality of their sensations after each stimulus using a list of descriptors (burning pain, cold pain, cramp-like, pricking, deep aching, pressure, other); they rated both the intensity of paradoxical pain and its unpleasantness according to two different 100 mm visual analog scales (VAS), graduated from "no pain" to "worst possible pain" and "not unpleasant" to "very unpleasant". Volunteers without any

paradoxical painful sensation or with inconsistent responses during the control period on the first experimental day (i.e. a difference in paradoxical pain intensity  $\geq 30\%$  between the two consecutive stimuli) were not included in the study.

iii) The intensity of the non-painful warm and cold sensations produced by two successive stimuli at temperatures used to evoke the paradoxical painful sensation. Even-numbered bars were kept at the neutral temperature and odd-numbered bars were set at the warm or the cold temperatures used to produce paradoxical pain, described above. Volunteers were asked to rate the intensity of their warm or cold sensations for each stimulus according to a 100 mm VAS graduated from "not warm" to "very warm" or "not cold" to "very cold".

iv) The intensity of normal pain evoked by one heat stimulus and one cold stimulus, above or below the heat and cold pain thresholds, respectively. Even-numbered bars were maintained at the neutral temperature and the temperature of the odd-numbered bars was set at  $2^{\circ}\text{C}$  above the heat pain threshold or  $2^{\circ}\text{C}$  below the cold pain threshold. Volunteers were asked to rate the intensity of pain for each stimulus on a 100 mm VAS graduated from "no pain" to "worst possible pain".

Pain thresholds (heat and cold) and the intensity of paradoxical pain were also determined 5 minutes after the administration of naloxone, using the procedure described above.

Blood pressure, heart rate and  $\text{SaO}_2$  were monitored during each session. Side effects such as nausea, vomiting, sedation, dysphoria and hallucinations were recorded when present. Volunteers were supervised for 2 hours after infusion.

#### *2.4 Statistical analysis:*

Results are expressed as means  $\pm 1$  SD. We compared changes, from baseline to after injection, in paradoxical pain intensity and unpleasantness (which



were our main criteria), pain thresholds, normal pain intensity and unpleasantness, intensity of non-painful sensations, between the active treatment and placebo. An analysis of variance (ANOVA), with Fisher's post hoc least significant difference test, was carried out in which the dependent variables were the outcome variables measured and the factors were treatment groups (morphine 0.025 mg/kg, morphine 0.1 mg/kg, placebo). We used the Wilcoxon signed ranks test to compare paired data measured at baseline between the experimental sessions (i.e. pain thresholds, warm and cold temperatures of the thermal grill, pain intensity). Pearson's correlation coefficient was used to analyse correlations between pairs of variables. Results were considered significant at  $P < 0.05$ .

### 3- RESULTS

Twenty volunteers were screened and 12 volunteers (six men and six women aged  $25 \pm 5$  years) completed the two sessions of the study. Eight volunteers were not included because either no paradoxical pain could be evoked or the intensity level recorded was inconsistent during the control period of the first experimental session. The mean doses of morphine administered intravenously were  $1.68 \pm 0.38$  mg for the lower dose (i.e. 0.025 mg/kg) and  $6.62 \pm 1.6$  mg for the higher dose (i.e. 0.1 mg/kg).

#### **3. 1 Effects of morphine on normal thermal pain**

##### *3.1. Heat and cold pain thresholds:*

The heat and cold pain thresholds measured before the administration of morphine or placebo were similar. Both the heat ( $F_{(2,33)} = 4.26$ ;  $p < 0.05$ ) and cold ( $F_{(2,33)} = 4.68$ ;  $p < 0.05$ ) pain thresholds were significantly changed after treatment. Post hoc analyses showed that, in comparison with placebo the administration of morphine 0.1 mg/kg induced a significant increase of the heat pain threshold ( $p < 0.05$ ) and a significant decrease (i.e. hypoalgesia) of the cold pain ( $p < 0.05$ ) (figure 1 A, B). These effects of morphine on thermal pain thresholds were partially reversed after administration of naloxone. In contrast, the changes in heat and cold pain thresholds after morphine 0.025 mg/kg were not significantly different from those induced by the placebo.

##### *3.1.2 Heat and cold pain evoked by stimuli above/below pain thresholds:*

Heat and cold stimuli above and below pain thresholds, respectively, evoked similar responses (i.e. pain intensity and unpleasantness) at baseline. Both 'normal' cold pain intensity ( $F_{(2,33)} = 6.81$ ;  $p < 0.01$ ) and unpleasantness ( $F_{(2,33)} = 5.04$ ;  $p < 0.05$ ) were significantly reduced after treatment. Heat pain intensity was not significantly changed ( $F_{(2,33)} = 1.48$ ; ns), while heat pain unpleasantness was significantly reduced

( $F_{(2,33)} = 3.59$ ;  $p < 0.05$ ). Post hoc analyses showed that, in comparison with the placebo, the administration of 0.1 mg/kg morphine, but not morphine 0.025 mg/kg, induced a significant reduction in both the intensity ( $p < 0.01$ ) and unpleasantness ( $p < 0.01$ ) of cold pain (figure 2 A, B), and in the unpleasantness of heat pain ( $p < 0.05$ ) (figure 2 C, D).

### **3. 2 Effects of morphine on paradoxical pain induced by the thermal grill:**

The warm and cool temperature combinations (i.e. temperatures of the thermal grill components) used to evoke paradoxical pain were similar at baseline between the low-dose morphine ( $40.2 \pm 2.4^\circ\text{C}$  and  $16.7 \pm 4.6^\circ\text{C}$ ), high-dose morphine ( $40.5 \pm 3.1^\circ\text{C}$  and  $16.9 \pm 5.4^\circ\text{C}$ ) and placebo groups ( $40.6 \pm 2.9^\circ\text{C}$  and  $17.4 \pm 4.1^\circ\text{C}$ ). Paradoxical pain was mostly (i.e. for 80% of the stimuli) described as burning pain. The temperatures of the warm and cool bars used to induce the paradoxical pain following treatment, adjusted to the new heat and pain thresholds, were:  $40.6 \pm 2.7^\circ\text{C}$  and  $15.8 \pm 4.7^\circ\text{C}$  in the low morphine group;  $41.2 \pm 3.1^\circ\text{C}$  and  $14.5 \pm 5.9^\circ\text{C}$  in the high morphine group and  $41.1 \pm 2.4^\circ\text{C}$  and  $16.7 \pm 4.2^\circ\text{C}$  in the placebo group.

Both the intensity ( $F_{(2,33)} = 3.84$ ;  $p < 0.05$ ) and unpleasantness ( $F_{(2,33)} = 5.97$ ;  $p < 0.01$ ) of paradoxical pain were significantly lower after treatment. Post hoc analyses showed that, in comparison with placebo, both paradoxical pain intensity ( $p < 0.05$ ) and unpleasantness ( $p < 0.01$ ) were significantly reduced after the administration of 0.1 mg/kg of morphine, but not after the administration of 0.025 mg/kg. This effect was reversed by the administration of naloxone (figure 3).

The effects of the high-dose (0.1 mg/kg) morphine on paradoxical pain intensity were directly correlated with its effects on the cold pain threshold ( $r = 0.66$ ;  $p < 0.01$ ) and normal cold pain intensity (i.e. induced by stimuli below the cold pain

threshold) ( $r = 0.72$ ;  $p < 0.01$ ). In contrast, there was no correlation between the effects of morphine on paradoxical pain and its effects on heat pain threshold ( $r = 0.35$ ; ns) or pain induced by suprathreshold heat stimuli ( $r = 0.33$ ; ns)

### ***3.3 Effects of morphine on non-painful thermal sensations corresponding to each of the components of the thermal grill***

None of the warm or cold only stimuli, set at temperatures used to evoke the paradoxical pain, were painful. Neither the warm ( $F_{(2,33)} = 0.43$ ; ns) nor cold ( $F_{(2,33)} = 0.2$ ; ns) sensations evoked by these stimuli were affected by treatment (figure 4).

### ***3.4 Side effects***

Five volunteers reported one or more side effects (nausea, sedation, dizziness) after the administration of morphine (0.1 mg/kg), one volunteer reported nausea after morphine (0.025 mg/kg) and one volunteer reported drowsiness after placebo. These side effects were all transitory, of mild intensity and none required specific treatment.

## Discussion

We showed that the paradoxical burning pain evoked by the simultaneous application of cold and warm stimuli with a thermal grill is reduced by morphine and reversed by naloxone. Thus, this "thermal grill illusion of pain" (TGIP) - a unique experimental illusion of pain - can be modified pharmacologically and may represent a new experimental model for testing analgesics.

Our findings complement our previous pharmacological study showing that TGIP can be selectively modified by a low dose of the NMDA receptor antagonist, ketamine<sup>22</sup>. In contrast, the morphine-induced reduction in paradoxical pain was associated with a reduction of normal pain. In particular, there was a correlation between the reduction in paradoxical pain and normal cold pain, suggesting that mechanisms of TGIP are related to those of physiological cold pain.

The mechanisms of the TGIP remain unclear. Although peripheral mechanisms have been proposed<sup>1</sup>, this phenomenon - which illustrates the interactions between the nociceptive and thermosensory systems - seems to depend primarily on central mechanisms. The best-documented hypothesis was proposed by Craig and Bushnell<sup>8</sup> on the basis of electrophysiological studies in animals and complementary psychophysical and neuroimaging data for humans<sup>11</sup>. They suggested that the thermal grill-induced paradoxical burning was due to a reduction of the physiological inhibition exerted by cold afferents in nociceptive pathways (probably at the thalamo-cortical level). This thermosensory disinhibition hypothesis was based on electrophysiological recordings from spinal dorsal horn neurones in the cat. It was shown that stimulation with the cold bars activated two populations of lamina I neurones: "COLD" cells, responding specifically to non-noxious cold stimuli, and multimodal "HPC" cells, activated by noxious heat and mechanical stimuli (i.e.

pinching) and by non-noxious cold stimuli below 25°C<sup>10</sup>. The addition of adjacent warm stimuli resulted in a reduction of the activity of COLD cells, but not of HPC neurons, so it was suggested that the burning pain induced by the grill resulted from changes in the pattern of the relative activities of the COLD and HPC neurones<sup>8</sup>. According to this thermosensory disinhibition theory, TGIP could be reduced either by inhibition of HPC neurons and/or by restoration of the inhibition of nociceptive pathways through increased COLD cell activity. Indeed, morphine can enhance the activity of COLD cells and suppress that of polymodal nociceptive cells (HPC)<sup>9</sup>. Consistent with some previous studies<sup>e.g.27</sup>, we found that morphine (0.1 mg/kg) selectively modified heat and cold pain without significantly altering the perception of non noxious thermal sensations. The absence of effect on cold sensation suggests that the activity of lamina I COLD cells - probably involved in cool sensation<sup>9</sup> - was not altered by morphine. Thus, the morphine-induced reduction of TGIP may be due to a reduction in the activity of HPC nociceptive neurons rather than the increased activity of COLD cells. The strong correlation between the reduction of TGIP and cold pain is also consistent with a reduced activity of HPC neurons. This correlation is also in line with the suggestion that the burning pain elicited by the thermal grill is similar to the burn of cold pain<sup>12</sup>. Indeed, the pattern of activity of spinal COLD and HPC neurons induced by the thermal grill is similar to that induced by a painful cold stimulus<sup>8</sup>. Functional neuroimaging data also suggest that similar mechanisms underlie these responses: the pattern of brain activation associated with TGIP<sup>11</sup> resembles that associated not only with normal (physiological) cold pain, but also cold allodynia in patients with neuropathic pain<sup>15,26</sup>.

Alternatively, TGIP may depend on the convergence and addition of the activity of adjacent cold and warm afferents on CNS multireceptive neurones

responding to both nociceptive and non-nociceptive stimuli<sup>4,19</sup>. This hypothesis and the thermosensory disinhibition theory are not mutually exclusive. Numerous cells with a very large range of responses to thermal stimuli (wide dynamic range (WDR) neurones) have been recorded in both the spinal cord and thalamus in rats, cats and primates<sup>2,5,6,21,28</sup>, although they rarely responded to both cool and warm stimuli<sup>23</sup>. Thus, the perceived distinction between the quality and intensity of thermal sensations may depend on the relative activities of the so-called "labelled sensory lines" (i.e. specific unimodal thermal pathways) and this multimodal intensity channel<sup>4,19</sup>. In line with this notion the reduced TGIP observed in our study may also result from the inhibition of WDR neurones by systemic morphine<sup>14,24</sup>. Animal studies may help further elucidate the neurophysiological mechanisms of the morphine-induced reduction of TGIP.

Thus, our findings, together with our previous results, demonstrate that TGIP may be a useful experimental model for pharmacological studies of analgesics in healthy volunteers. The differential effects observed for ketamine and morphine, suggesting distinct mechanisms of action, demonstrated that this phenomenon is sensitive to both antinociceptive and antihyperalgesic drugs. One advantage of TGIP is that it represents a totally harmless and, therefore, ethically acceptable pain model.

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Figure 1: Heat and cold pain thresholds measured before and after the administration of 0.1 mg/kg morphine (black columns), 0.025 mg/kg morphine (hatched columns) or placebo (white columns). High-dose morphine (0.1mg/kg) significantly increased the heat pain threshold and significantly decreased (i.e. hypoalgesia) the cold pain threshold. \*,  $p < 0.05$ .

Figure 2: Effects of morphine of the intensity and unpleasantness of normal pain induced by suprathreshold cold (A, B) or suprathreshold heat (C, D) stimuli. Cold pain intensity and unpleasantness and heat pain unpleasantness, were significantly lower after high-dose morphine (0.1mg/kg) treatment (black columns) than after placebo (white columns). In contrast, no significant effects were observed after 0.025 mg/kg morphine (hatched columns). \*,  $p < 0.05$ ; \*\*,  $p < 0.01$ .

Figure 3: Effects of morphine of the intensity and unpleasantness of paradoxical pain induced by a thermal grill.

Both the intensity (A) and unpleasantness (B) of paradoxical pain were significantly lower after administration of 0.1 mg/kg morphine (black columns), than after placebo (white columns). This effect was partially reverse by naloxone. Low-dose (0.025 mg/kg) morphine (hatched columns) had no significant effect. \*\*,  $p < 0.01$ .

Figure 4: Effects of morphine on non-painful warm or cold thermal sensations induced by stimuli at the temperatures used to evoked paradoxical pain (i.e. components of the thermal grill). No significant change in thermal sensations (i.e. VAS scores) were observed following administration of 0.1 mg/kg morphine (black columns), 0.025 mg/kg morphine (hatched columns) or placebo (white columns).

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