Effect of riluzole on acute pain and hyperalgesia in humans

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Riluzole modulates several transmitter systems which may be involved in nociception. Antinociceptive effects have been shown in animal studies, but there are no human data. Therefore, we have examined the acute analgesic effect of riluzole in a human model of inflammatory pain induced by a thermal injury on the distal leg (47°C, 7 min, 12.5 cm²) in 20 healthy volunteers. Hyperalgesia to mechanical and heat stimuli were examined by von Frey hairs and thermodes. We used a randomized, double-blind, placebo-controlled design, and subjects received riluzole 100 mg or placebo for 2 days with a 14-day interval. The burns produced significant hyperalgesia, but riluzole had no acute analgesic effects in normal or hyperalgesic skin.

Keywords: pain, acute; pain, experimental; model, pain; pharmacology, riluzole

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Riluzole (2-amino-6-trifluoromethoxybenzothiazole, Rilutek, Rhone-Poulenc Rorer, Antony Cedex, France) is a novel drug used in the treatment of amyotrophic lateral sclerosis (ALS). It has neuroprotective, anticonvulsive and sedative properties, but the mechanisms of action are not fully understood. Several effects have been demonstrated, including inhibition of glutamate release, indirect antagonism of excitatory amino acid receptors, stabilization of inactivated sodium channels and inhibition of presynaptic γ-aminobutyric acid (GABA) reuptake. These mechanisms are believed to be involved in the perception of pain, because N-methyl-D-aspartate (NMDA) receptors and glutamate release are involved in central hyperexcitability and inhibition of sodium channels may be an important mechanism underlying the analgesic effects of drugs such as i.v. lidocaine in the treatment of neuropathic pain. Furthermore, GABAergic mechanisms in the spinal cord exert tonic inhibition of nociceptive inputs via both GABA_A and GABA_B receptors. Thus inhibition of GABA reuptake may induce analgesic effects.

Riluzole induces a hypnotic state and potentiates the hypnotic effect of thiopental and ketamine in rats. Local anaesthetic effects of riluzole have been demonstrated after intradermal injection and local application in the lacrimal sac in animal studies. However, no effect on nociceptive thresholds was observed after i.v. administration of riluzole 3 mg kg⁻¹ in rats. As no study has investigated the analgesic effect of riluzole in humans, we examined riluzole in a human model of inflammatory pain. Riluzole was administered as a single dose as this design is most relevant when considering pre-traumatic administration of analgesics. The dose was based on the 24-h dose which is used solely in the treatment of patients with ALS.

Subjects and methods

We studied 20 healthy volunteers (17 males), aged 22–48 yr. Informed consent was obtained from all subjects and the study was approved by the Municipal Ethics Committee of Copenhagen. During a pre-study training session, subjects were asked about their general health, underwent a physical examination, experienced the burn and were trained in all assessments performed during the study.

The study used a randomized, double-blind, placebo-controlled, crossover design. Each volunteer received riluzole 100 mg orally as a single dose or placebo on 2 study days separated by 2 weeks. The order of the study days was randomized en bloc; treatments were equally distributed over the first and second days. The drug was administered after baseline measurements were obtained, and observations were repeated 75 min later. Subjects fasted from the night before to ensure even uptake of riluzole. The burn was induced 90 min after administration of riluzole, at the time when maximum plasma concentrations of riluzole were expected, and observations were made 0, 1, 2 and 3 h after the burn. The order and duration of these observations have been described previously. All testing was performed by two investigators in a quiet room with a temperature of 23–26°C and a relative humidity of 40–64%. Each subject was tested by the same investigator on the 2 study days, and the assessments were made at the
same time of the day. Subjects were resting in a relaxed position and were instructed to keep their eyes closed during all measurements.

Burns were produced on the medial part of the non-dominant distal leg with a 50×25 mm thermode (Thermotest, Somedic A/B, Stockholm, Sweden). The burns were induced in the same area on the 2 study days. The thermode (47°C) was applied to the skin for 7 min under standardized pressure (6.9 kPa). This caused redness without blistering.

Pain was rated using a visual analogue scale (VAS 0–100), at the start and every minute during heat injury. The scale was anchored by the descriptors, no pain (0) and worst pain imaginable (100). Verbal descriptors were added at 2 mm (weak pain), 8 mm (mild pain), 18 mm (moderate pain), 39 mm (strong pain) and 75 mm (very intense pain), to make the scale more comprehensible. The subjects rated the pain with a slider on a plastic device that was pulled along a 10-cm line between end-points. The numeric value of the rating was read on the back of the device by the investigator.

Mechanical pain threshold within the injury area was determined by pinprick with nine progressively rigid von Frey hairs (Senselab Aesthesiometer, Somedic A/B, Stockholm, Sweden) numbered 1–9 (force of hairs: hair No. 1 = 7 mN, No. 2 = 9 mN, No. 3 = 17 mN, No. 4 = 25 mN, No. 5 = 45 mN, No. 6 = 73 mN, No. 7 = 132 mN, No. 8 = 211 mN, No. 9 = 279 mN). Suprathreshold pain responses to mechanical stimuli were assessed by five stimuli of 423 mN. The area of mechanical hyperalgesia to punctate stimuli that developed around the burn area was assessed using a rigid von Frey hair (423 mN), and the area of allodynia was assessed by gently stroking the skin with a fingertip. Heat pain thresholds were determined using a computerized contact thermode (Somedic A/B, Stockholm, Sweden). The thresholds were assessed using a 25×50 mm thermode and determined as the average of three trials performed at 9-s intervals, from a baseline temperature of 32°C and with a rate of change of 1°C s⁻¹. The upper cut-off limit was 52°C. The pain response (VAS 0–100) to heat was evaluated with a heat stimulus (15×25 mm thermode) of 45°C lasting 5 s, preceded by an increase in temperature from 40 to 45°C over 5 s. The pain response to a prolonged (80 s) heat stimulus was also tested, but only 2 h after the burn. The heat stimulus (25×50 mm) was increased in steps of 1°C every 20 s from 44 to 47°C. Pain was rated after 15 s at each temperature.

Subjects completed a questionnaire at the end of each day concerning the presence of abdominal pain, perioral paraesthesia, palpitations, nausea, drowsiness and dizziness. When side effects were present, these were rated as weak, moderate or marked.

Statistical analysis
Normality of data and differences between groups were evaluated using the Shapiro–Wilk’s W test. Data are presented as means or medians, depending on the distribution (normal or skewed), and comparisons were made using the Student’s t test for a paired design, when the differences showed normal distribution, whereas differences showing non-normal distribution were analysed using the Wilcoxon test for paired observations. Comparisons between riluzole and placebo for the post-burn period were based on the mean of the 0, 1, 2 and 3 h measurements. The overall effect of riluzole on post-burn pain was evaluated by combining all pain measurements (heat pain detection, mechanical pain detection, mechanical pain in the burn area, mechanical pain outside the burn area, secondary hyperalgesia and pain responses to 45°C) in a single measure. Each measurement was converted to percentage of maximum possible effect (%MPE = (post-drug value–baseline)×100/(cut-off value–baseline)). Comparisons of more than two groups (e.g. changes over time) were made using parametric analysis of variance (ANOVA) for repeated measurements (one-way) or the Friedman ANOVA, as appropriate. The smallest differences between riluzole and placebo detectable with the present variation, a power of 80% and a type I error of 5%, were calculated for all measurements at all times. P<0.05 was considered statistically significant.

Results
Baseline and post-drug assessments were not significantly different between the two groups. The pain response (VAS 0–100) to the burn was not significantly altered by riluzole (Fig. 1A). In 13 of 20 subjects, allodynia developed around the burn injury area when tested 4–6 min after the start of the burn. The areas of allodynia were not reduced by riluzole (mean 38 (range 0–120) cm²) compared with placebo (34 (0–103) cm²).

The burn decreased mechanical pain thresholds (P<10⁻⁵, Friedman ANOVA) and increased pain responses to mechanical stimuli within the site of injury (P<10⁻⁵, Friedman ANOVA) (Fig. 2A, B). Neither the pain threshold nor the suprathreshold pain response was altered significantly by riluzole compared with placebo. For both placebo and riluzole treatment, the burn produced a significant area of hyperalgesia to punctate mechanical stimuli around the injury (P<10⁻⁵, Friedman ANOVA), and increased the pain response to mechanical stimuli in the area of secondary hyperalgesia (P<10⁻⁵, Friedman ANOVA) (Fig. 3A, B); there were no differences between riluzole and placebo.

For both treatments, pain responses to 45°C (5 s) were increased by the burn (P<10⁻⁴, Friedman ANOVA), and heat pain thresholds were decreased in the burn area (P<0.0007, one-way ANOVA). Pain during prolonged (44–47°C) or brief (45°C) heat stimuli was not reduced by riluzole, and the heat pain threshold was not increased significantly by riluzole compared with placebo (Figs 1B, 4A, B).

The total post-burn pain response based on six pain
Fig 1 Median pain during burn (47°C for 7 min) (A) and median pain response to a stepped heat stimulus (44–47°C for 80 s) (B) in the placebo and riluzole groups. Verbal descriptors were added to the VAS (weak pain 2%, mild pain 8%, moderate pain 18%, strong pain 39% and very intense pain 75%). Neither the pain response to the burn nor the pain response to a prolonged heat stimulus in hyperalgesic skin was significantly reduced by riluzole compared with placebo.

Fig 2 Median mechanical pain detection thresholds (A) and median mechanical pain in the burn area (B) in the placebo and riluzole groups. Neither the pain threshold nor the suprathreshold pain response was altered significantly by riluzole compared with placebo.

Fig 3 Median area of secondary hyperalgesia (A) and median mechanical pain in the secondary hyperalgesic area (B) in the placebo and riluzole groups. Neither the area of secondary hyperalgesia nor the pain response to mechanical stimuli within the zone of secondary hyperalgesia was significantly decreased by riluzole compared with placebo.

measures (heat pain detection, mechanical pain detection, mechanical pain in the burn area, mechanical pain outside the burn area, secondary hyperalgesia and pain responses to 45°C) was not altered significantly by riluzole compared with placebo ($P\leq0.11$, Wilcoxon matched pairs test).

The smallest differences between placebo and riluzole detectable at single times are presented in Table 1. Values are the mean of six observation times (baseline, post-drug, 0, 1, 2 and 3 h post-burn).

Two volunteers reported drowsiness after riluzole whereas three reported drowsiness after placebo. None of the subjects experienced abdominal pain, perioral paraesthesia, palpitations, nausea or dizziness. One person reported headache after placebo. No other side effects were reported.

**Discussion**

We have examined the analgesic effect of riluzole compared with placebo in a model of inflammatory pain based on a standardized burn injury in healthy volunteers. We found that riluzole did not reduce pain significantly in either normal or hyperalgesic skin. Several molecular effects of riluzole have been demonstrated. At the presynaptic level it inhibits the release of glutamate and reuptake of GABA. At the postsynaptic level it inhibits responses evoked by
Effects of riluzole on acute pain and hyperalgesia

Excitatory amino acids and stabilizes inactivated sodium channels. These mechanisms may be of major importance for nociceptive transmission as NMDA receptors and glutamate release mediate sensitization of neurones in nociceptive pathways and inactivation of sodium channels relieves some neuropathic and acute pain states, as demonstrated with the use of systemic local anaesthetics. GABA is believed to be involved in the descending control of pain from higher centres in the CNS and GABAergic mechanisms exert tonic inhibition of nociceptive inputs via both GABA A and GABA B receptors.

Preliminary studies in guinea pigs and rabbits have demonstrated a local anaesthetic effect of riluzole in high concentrations. In guinea pigs, riluzole produced local anaesthesia, evaluated by the twitch reflex to pinprick, 15 min after intradermal application, with a median effective concentration (EC 50 ) of 43 mmol litre −1 . In rabbits, riluzole produced local anaesthesia evaluated by the blink reflex in response to touching the cornea 15 min after local application in the lacrimal sac, with an EC 50 of 3 mmol litre −1 .

However, no effect on nociceptive thresholds in rats was observed after riluzole 3 mg kg −1 i.v. Mantz and colleagues showed that systemic riluzole induced loss of the righting reflex (ability to right from a lateral position) in rats with a median effective dose of 26 mg kg −1 , and riluzole prolonged the hypnotic effects of ketamine and thiopental. Thus preliminary animal studies suggest local and general anaesthetic effects of riluzole.

Our study is the first to examine the analgesic effects of riluzole in humans, and our data do not support the existence of an important acute analgesic effect. Our negative results may be explained by the dose, sensitivity of the study and possibility that riluzole has no effect on acute inflammatory pain induced by a burn injury to skin.

Riluzole was administered orally 90 min before the burn and all subjects were fasted to ensure even uptake of riluzole. Maximum plasma concentrations are reached 60–90 min after oral administration and the half-life is 9–15 h. Therefore, it seems unlikely that the measurements were made either too early or too late. Riluzole was administered as a single dose of 100 mg, which is the dose used in the treatment of patients with ALS (50 mg bid). 20 The distribution volume of riluzole is 3.4 litre kg −1 and the absolute bioavailability is 60%. This gives a maximum tissue concentration of approximately 1.08 µmol litre −1 after 100 mg, and pharmacokinetic studies show that the maximum plasma concentration after 50 mg of oral riluzole is 0.91 (so 0.39) µmol litre −1 . Thus the negative result may be explained by insufficient dose, as these concentrations are well below those demonstrated in experimental studies to have local anaesthetic effects (43 000 and 3000 µmol litre −1 ). However, a human study using substantially larger doses would not be clinically relevant because of side effects.

We cannot exclude a minor analgesic effect of riluzole, as we were just able to detect differences between riluzole and placebo of approximately 30% with a power of 80%. Further, the absence of analgesic effects in the present model does not exclude analgesic effects in neuropathic and visceral pain states. However, our study excludes important acute analgesic effects of riluzole in normal and hyperalgesic skin in humans, and the only animal study using a comparable dose (3 mg kg −1 ) showed no effect on nociceptive thresholds in rats.

In summary, riluzole 100 mg had no significant acute analgesic effect in either normal skin or hyperalgesic skin induced by a standardized burn injury in healthy volunteers.

Table 1 The smallest detectable differences between placebo and riluzole with a power of 80% and a type I error of 5%. Values are the mean of six observation times (baseline, post-drug, 0, 1, 2 and 3 h post-burn).

<table>
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<tr>
<th>Pain during burn (VAS 0–100)</th>
<th>Heat pain response to 44–47°C for 5 s (VAS 0–100)</th>
<th>Heat pain threshold (°C)</th>
<th>Heat pain response to 45°C for 5 s (VAS 0–100)</th>
<th>Mechanical pain in burn area (VAS 0–100)</th>
<th>Mechanical pain threshold (von Frey No.)</th>
<th>Area of secondary hyperalgesia (cm 2 )</th>
<th>Mechanical pain in zone of secondary hyperalgesia (VAS 0–100)</th>
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<tr>
<td>7</td>
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<td>1.1</td>
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<td>3</td>
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