Effects of Radolmidine, A Novel \( \alpha_2 \)-Adrenergic Agonist Compared with Dexmedetomidine in Different Pain Models in the Rat

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Background: Intrathecally administered \( \alpha_2 \)-adrenoceptor agonists produce effective antinociception, but sedation is an important adverse effect. Radolmidine is a novel \( \alpha_2 \)-adrenoceptor agonist with a different pharmacokinetic profile compared with the well-researched dexmedetomidine. This study determined the antinociceptive and sedative effects of radolmidine in different models of acute and chronic pain. Dexmedetomidine and saline served as controls.

Methods: Male Sprague-Dawley rats were studied in acute pain (tail flick), carrageenan inflammation, and the spinal nerve ligation model of neuropathic pain. Mechanical allodynia was assessed with von Frey filaments, cold allodynia with the acetone test, and thermal hyperalgesia with the paw flick test. Locomotor activity–vigilance was assessed in a dark field. Dexmedetomidine and radolmidine were administered intrathecally in doses of 0.25 \( \mu \)g, 2.5 \( \mu \)g, 5 \( \mu \)g, and 10 \( \mu \)g.

Results: In the tail flick test, radolmidine showed a dose-dependent antinociceptive effect, being equipotent compared with dexmedetomidine. In carrageenan inflammation, intrathecal doses of 2.5 \( \mu \)g or 5 \( \mu \)g of dexmedetomidine/radolmidine produced significant antinociception compared with saline (P < 0.01). The two drugs were equianalgesic. In the neuropathic pain model, an intrathecal dose of 5 \( \mu \)g dexmedetomidine–radolmidine had a significant antiallodynic effect compared with saline (P < 0.01). The two drugs were equipotent. Intrathecal administration of both dexmedetomidine and radolmidine dose dependently decreased spontaneous locomotor activity–vigilance, but this effect was significantly smaller after intrathecal administration of radolmidine than after intrathecal dexmedetomidine.

Conclusions: Radolmidine and dexmedetomidine had equipotent antinociceptive effects in all tests studied. However, radolmidine caused significantly less sedation than dexmedetomidine, probably because of a different pharmacokinetic profile. (Key words: Inflammation; neuropathy; spinal.)

INTRATECAL administration of \( \alpha_2 \)-adrenoceptor agonists produces antinociception in laboratory animals and analgesia in humans. Dexmedetomidine, a selective and specific \( \alpha_2 \)-adrenoceptor agonist, has been shown to produce antinociception at the spinal cord level in behavioral tests and also in single cell recordings from the spinal cord during noxious electrical stimulation of the receptive fields. Intrathecally administered dexmedetomidine has also reversed nerve ligation–induced allodynia. Intracerebroventricular and intrathecally administered \( \alpha_2 \)-adrenoceptor agonists have produced dose-dependent sedation. Sedation has been a common problem with the currently available \( \alpha_2 \)-adrenoceptor agonists after both systemic and spinal administration.

As a lipophilic agent, dexmedetomidine is rapidly absorbed into blood circulation and causes systemic effects even after intrathecal administration. The novel \( \alpha_2 \)-adrenoceptor agonist radolmidine (2,3-dihydro-3-(1H-imidazol-4-ylmethyl)-1H-indan-5-ol-hydrochloride), like dexmedetomidine, is a full agonist at all \( \alpha_2 \)-adrenergic receptors. However, it has a different pharmacokinetic profile with less activity to cross the blood–brain barrier and with less rapid distribution within the central nervous system. The present series of studies was designed to characterize radolmidine in comparison with dexmedetomidine in various pain models representing both acute and chronic nociception. In addition, the effects of

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Received from the Department of Pharmacology and Toxicology, Institute of Biomedicine, University of Helsinki, and the Pain Relief Unit, Department of Anaesthesia, Helsinki University Hospital, Helsinki, Finland. Submitted for publication November 22, 1999. Accepted for publication March 15, 2000. Supported by the European Union Biomed 2 contract BMH4 CT 95 0172, Helsinki, Finland, the Finnish Cultural Foundation, Helsinki, Finland, the Finnish Academy of Sciences, Helsinki, Finland, and Orion Corporation, Turku, Finland. Presented in part at the 9th International Association for the Study of Pain (IASP) World Congress on Pain, Vienna, Austria, August 22, 1999.

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intrathecal injection of radolmidine and dexmedetomidine on locomotion–vigilance were assessed in this study.

**Materials and Methods**

**Animals**

Male Sprague-Dawley rats (Bk:SD; B&K Universal Ab, Sollentuna, Sweden) weighing 150–175 g in the beginning of the experiment were used. Laboratory chow (R36; Lactamin Specialföretaget, Stockholm, Sweden) and water were available ad libitum. Rats were housed in groups of five in plastic cages in artificial lighting with a fixed 12-h light–dark cycle. Guidelines for animal research by local authorities and the International Association for the Study of Pain were adhered to, and the study protocol was approved by the institutional animal investigation committee.

**Drugs**

Dexmedetomidine was used as a control compound to study the effects of the new α2-adrenergic agonist radolmidine. Atipamezole, the selective α2-adrenoceptor antagonist, was used to reverse the effects. Atipamezole, dexametomidine, and radolmidine were provided by Dr. Raimo Virtanen, Orion Corporation, Turku, Finland. Saline served as an inactive control.

**Experimental Procedures**

**Intrathecal Cannulation.** For the insertion of the intrathecal cannula, rats were anesthetized with a subcutaneous injection of midazolam 5.0 mg/kg (Dormicum; Roche, Basle, Switzerland) and 1.0 ml/kg of the mixture of fentanyl 0.2 mg/ml and fluanisone 10 mg/ml (Hypnorm; Janssen Pharmaceutica, Beerse, Belgium). A thin polyethylene cannula (PE-10; Meadox Surgimed A/S, Stenløse, Denmark) was inserted through the cisterna magna into the lumbar subarachnoid space, 8 cm from the insertion, and fixed with a suture to the paravertebral muscles. After cannulation the animals were housed individually in standard Plexiglass cages. To verify the proper placement of the cannula, 10 μl of 5% hyperbaric lidocaine (Lidocain Pond, Medipolar, Oulu, Finland) was injected. Only rats that developed reversible symmetrical paralysis of both hind limbs and the tail after the injection of lidocaine were used in the experiments.

**Inflammatory Pain: Carrageenan-induced Hind Paw Inflammation.** The rats were anesthetized with halothane, and λ-carrageenan (Sigma, St. Louis, MO) 0.2 mg in 0.1 ml of saline was injected into the palm of the left hind paw 2 h before the behavioral measurements were begun.

**Neuropathic Pain Model: Ligation of Spinal Nerves.** The model of neuropathic pain introduced by Kim and Chung in 1992, the spinal nerve ligation model, was used. In brief, the animals were anesthetized with 1% halothane (Trothane, ISC Chemicals, Bristol, United Kingdom) in N2O and O2 (70%:30%). The left L5 and L6 spinal nerves were exposed by removing a small piece of the paravertebral muscle and a part of the left spinous process of the L5 lumbar vertebra. The L5 and L6 spinal nerves were then carefully isolated and tightly ligated with 6-0 silk. After checking hemostasis, the muscle and the adjacent fascia were closed with sutures, and the skin was closed with metal clips.

**Tests for Allodynia, Hyperalgesia, and Thermal Nociception.** The rats were always habituated to handling, and the testing equipment (30 min of handling per day for 3 days) before the experiments. Thermal nociception (noxious heat) was tested with the tail flick apparatus (Ugo Basile, Comerio, Italy) with a cutoff time of 8 s to prevent tissue damage. The animals were restrained in transparent Plexiglass tubes during the tail flick tests. Tail flick results are expressed as percentage of the maximum possible effect (MPE%) calculated with the following formula:

\[
\text{MPE\%} = \frac{\text{postdrug latency} - \text{predrug latency}}{\text{cutoff latency} - \text{predrug latency}} \times 100\%
\]

The tail flick test was also used to determine whether the selective α2-adrenergic antagonist atipamezole (100 μg administered intrathecally) could reverse the antinociceptive effect of radolmidine (3 μg administered intrathecally). Atipamezole was administered either 15 min before or after radolmidine.

Heat hyperalgesia was tested with the paw flick test apparatus (Ugo Basile). The stimulus intensity was set at 40 (arbitrary units on a scale of 0–90). The cutoff time was 16 s to prevent tissue damage. The measurements were performed on both hind paws three times at each time point. The stimulus was begun only when the tested paw was set on the glass floor of the device.

Threshold for mechanical allodynia was measured with a series of von Frey filaments (Semmes-Weinstein monofilaments, Stoelting, IL). The rats were standing on a metal mesh covered with a plastic dome. The plantar surface of the paw was touched with different von Frey filaments with a bending force from 0.217 to 12.5 grams (g) until the threshold force that induced paw withdrawal in more than half of the stimuli was
found. The testing was begun by seeking the allodynic areas of the ventral surface of the paw with the von Frey filament of 12.5 g. If the rat responded to the stimulation with a paw withdrawal, the next lighter filament was used until the threshold was found. To avoid excessive stimulation, the probing was started in the following testing sessions with the weakest filament that had elicited withdrawal responses in the previous session. If the strongest filament did not give a response, 12.5 g was recorded as the threshold. Higher forces should not be used with this method, because the paw would be lifted up by the testing stimulus even in a normal animal.17

Cold allodynia was measured as the foot withdrawal response after application of acetone to the plantar surface of the paw.18 The rats were standing on a metal mesh. A drop of acetone was gently applied to the heel of the rat with a syringe connected to a thin polyethylene tube. A brisk foot withdrawal response after the spread of acetone over the plantar surface of the paw was considered as a sign of cold allodynia. The testing was started with the paw contralateral to the nerve injury and repeated five times for both paws with an interval of approximately 2 min between each test.

**Temperature.** The temperature of both the neuropathic (left) and nonneuropathic (right) paws was measured to determine if the neuropathy changes the baseline temperature of the paw and if the studied drugs have different effects on the temperature of the affected and nonaffected paws. The temperatures were measured using a Tempett infrared thermometer (Senselab, Stockholm, Sweden) before the drugs were given and at 30 and 60 min from the intrathecal injection of saline, dexmedetomidine (0.5, 2.5, 5.0 µg), and radolmidine (0.5, 2.5, 5.0 µg).

**Spontaneous Locomotor Activity.** Spontaneous locomotor activity was assessed in a dark field with an automatic measurement system (Kungsbacka Mät- & Reglerteknik AB, Kungsbacka, Sweden). The rats were placed in a sound isolated box (70 × 70 × 35 cm) that had two series of photocells located 2 cm and 12 cm above the floor, and the cover of the box was closed to isolate it from ambient light and noises. The lower series of photocells detected movement of the animal as crossing of the photocell lines and the upper photocells registered rearing. Six 5-min measurement periods were used to cover a 30-min assessment time. Decrease in spontaneous locomotor activity could reflect, for example, motor dysfunction or sedation. For the dose-response curve, mean percentage of inhibition at 0–15 min after the drug administration was calculated as the mean of:

\[ \text{MPE\%} = \frac{\text{mean} \times (\text{AUC}_{\text{drug}, 0-15} - \text{AUC}_{\text{drug}, 15-30})}{\text{mean} \times (\text{AUC}_{\text{sal}, 0-15})} \times 100\% \]

where AUC drug,0-15 is the area under the curve from 0 to 15 min after the drug administration, and (AUCsal,0-15) is the area under the curve from 0 to 15 min after the injection in the saline control group.

**Statistical Analysis**

Continuous normally distributed variables, such as the paw temperature, were analyzed using analysis of variance or analysis of variance for repeated measures, as appropriate. Variables that did not fulfill these criteria, e.g., the mean percent of inhibition in the activity test, were analyzed using the Mann–Whitney U test.

**Results**

**Acute Nociception**

In the tail flick test, intrathecal administration of radolmidine and dexmedetomidine produced clear dose-related antinociception with a maximum effect at 30 min (fig. 1). The two drugs were equipotent. The maximum antinociceptive effect represented by a nearly 100% MPE was achieved with 10 µg radolmidine. The antinociceptive effect was significantly different from the saline group from 15 to 60 min in both groups (P < 0.001).

The antinociceptive effect of 3 µg intrathecal radolmidine was significantly reduced when atipamezole was given either before or after radolmidine. The MPE% of the tail flick latency after 3 µg intrathecal radolmidine was reduced from 72% to 12% at 15 min after pretreatment with 100 µg of atipamezole compared with saline (P = 0.002). When atipamezole was given 15 min after the administration of 3 µg intrathecal radolmidine, the MPE% of the tail flick latency decreased from 80% to 16%, whereas it increased from 70% to 87% after saline (P < 0.001).

**Inflammatory Pain**

Carrageenan inflammation produced both mechanical allodynia and heat hyperalgesia (figs. 2A and 2B). The mean predrug thresholds for the von Frey filaments were approximately 4 g compared with > 12.5 g in the normal rat. Dexmedetomidine and radolmidine decreased mechanical allodynia as measured with von Frey filaments in the inflamed paw in a dose-dependent fashion (fig. 2C). The thermal hyperalgesia in the paw flick test...
was also reduced with both drugs (fig. 2D). The peak antiallodynic effect in the mechanical test was observed at 30–45 min (fig. 2A), whereas the maximum increases in the paw flick latencies were detected at 15 min (fig. 2B). The dose–response curves showed that the two drugs had very similar antiallodynic and antihyperalgesic effects in the carrageenan model (figs. 2C and 2D).

### Neuropathic Pain

The animals that responded to a von Frey filament force < 12.5 g and with at least one positive response in the acetone test were considered to have neuropathic symptoms and were eligible to enter the study. Thus, 70% of the rats could be included. The low thresholds for mechanical stimulation and significant cold allodynia produced by the neuropathy can be seen in the predrug values in figures 3A and 3B. A normal rat would not respond to acetone stimuli. Heat hyperalgesia was not evident as the paw flick latencies in the ipsilateral and contralateral paws were comparable (data not shown).

Both dexmedetomidine and radolmidine in intrathecal doses of 0.5, 2.5, and 5.0 µg had a significant dose-dependent antiallodynic effect at 30 min when tested with von Frey filaments (P < 0.01; figs. 3A and 3C). In the acetone test, dexmedetomidine and radolmidine had a significant dose-dependent antiallodynic effect compared with saline (P < 0.01; figs. 3B and 3D). Cold allodynia was virtually abolished by 30 min. In the paw flick test, dexmedetomidine and radolmidine in an intrathecal dose of 5.0 µg increased the paw flick latency in both paws (data not shown). The maximum effect was reached 30 min after intrathecal administration. The two drugs were equipotent. The neuropathy model that was used did not alter the temperature of the affected paw as compared with the contralateral paw (results not shown). The temperatures in either of the paws were not significantly affected by any of the doses of the drugs tested (results not shown).

### Spontaneous Locomotor Activity

In the locomotor activity measurements, intrathecal administration of both dexmedetomidine and radolmidine dose dependently decreased spontaneous locomotor activity (fig. 4). However, this effect was significantly smaller after intrathecal administration of radolmidine than after intrathecal dexmedetomidine (fig. 4; P < 0.001 for 2.5 µg, P = 0.012 for 5 µg, and P = 0.03 for 10 µg, when the percent of inhibition at 0–15 min after the drug administration produced by radolmidine was compared with that of dexmedetomidine).

### Discussion

α₂ Adrenoceptors are found in the dorsal horn of the spinal cord and in multiple areas of the brain. The antinociceptive effects of spinally and systemically administered α₂-adrenergic agonists have been verified with a number of agonists in different pain models in both animals and humans. The spinal site of action is crucial for the antinociceptive effect, as intrathecally administered α₂-adrenergic agonists produce antinoci-
ception in much lower doses than what is needed for an effect after systemic administration. In addition, transection of the spinal cord does not abolish the antinociceptive effect of systemically administered $\alpha_2$-adrenergic agonists. Recent studies further support the conclusion that the supraspinal sites do not play an important role in $\alpha_2$-adrenoceptor-mediated antinociception, although contradicting views have also been proposed.

Like dexmedetomidine, radolmidine is a highly potent, specific and selective $\alpha_2$-adrenergic agonist showing full agonist efficacy on all three $\alpha_2$ adrenoceptors ($\alpha_{2A}$, $\alpha_{2B}$, $\alpha_{2C}$). Recently, Eisenach et al. showed that intrathecal radolmidine produced antinociception to a mechanical stimulus in a sheep model of acute pain. The ED$_{50}$ of radolmidine was approximately 30% less than that of dexmedetomidine in sheep. Previously, dexmedetomidine has been shown to be effective in acute nociception as evidenced by increases in hot plate and tail flick latencies. In the present study, radolmidine and dexmedetomidine were equipotent in the tail flick test. A 50% MPE was achieved with approximately 1 $\mu$g radolmidine, and 10 $\mu$g produced a 100% effect. In addition, the duration of the effect was comparable after the two drugs. The antinociceptive effects of radolmidine were reversed by 80% with atipamezole 100 $\mu$g, indicating that the antinociceptive effect was mediated by $\alpha_2$ adrenoceptors.

Carrageenan-induced inflammation causes edema of the paw and enhanced sensitivity of the paw toward both thermal and mechanical stimuli. Intrathecal administration of dexmedetomidine has been shown to increase paw pressure thresholds and tail flick latencies in both the control rats and those with unilateral carrageenan inflammation. In the present study, both radolmidine and dexmedetomidine increased paw flick latencies and thresholds for von Frey filament forces in the inflamed paw. Radolmidine and dexmedetomidine were equianalgesic. Interestingly, lower doses of radolmidine were needed to reverse mechanical compared with thermal hyperalgesia. However, the antihyperalgesic doses of the $\alpha_2$-adrenergic agonists were in the same range as those showing efficacy in the tail flick test, whereas opioids can reverse inflammation-induced thermal hyperalgesia in doses that are not effective against noxious heat.

The ligation of the spinal nerve L5–L6 paravertebrally
leads to reliable and prominent tactile allodynia. Mechanical and cold allodynia were also clear in the present experiments. The paw flick latencies were almost identical in the ipsilateral and contralateral paws, indicating lack of thermal hyperalgesia in this model of neuropathic pain. In previous studies in which heat hyperalgesia has been present, it has clearly been a less significant symptom than mechanical or cold allodynia. A decrease of approximately 20% in the paw flick latency of the ipsilateral as compared with the contralateral paw has been described, whereas in mechanical allodynia there is a greater than 100-fold decrease in the force inducing paw withdrawal. Normal rats do not show any cold allodynia. The spinal nerve ligation model has an important feature in being one of the least opioid sensitive of the many neuropathic pain models. Surgical sympathectomy has been shown to reduce this allodynic state. The spinal nerve ligation model thus bears a close resemblance to the clinical neuropathic pain, which often is poorly opioid responsive, shows cold allodynia, and may also be maintained by the activity of the sympathetic nervous system. Previous studies have already indicated that α₂-adrenergic agonists are effective in this opioid-insensitive pain model. It has also been suggested that the endogenous α₂-adrenergic system may be important in controlling the neuropathic symptoms as atipamezole, the selective α₂-adrenergic agonist, has kindled allodynia in nerve-injured animals that do not initially display cold or tactile allodynia. In agreement with this, both ralodidine and dexmedetomidine produced dose-related antiallodynic effects. The antiallodynic doses were lower than those needed for antinociceptive effects in the tail flick test. Cold allodynia was already significantly reduced with the lowest doses tested, 0.5 μg. Porge et al. also showed that the analgesic potency of dexmedetomidine is enhanced after nerve injury. However, these investigators administered dexmedetomidine systemically and suggested that the effect could be peripheral.

This increased efficacy of α₂-adrenergic agonists against allodynia in the spinal nerve ligation model could be mediated via release of acetylcholine. Intrathecally administered clonidine increases concentrations of acetylcholine in microdialysates from spinal cord dorsal
Recently, Pan et al. showed that the antiallo-
dynic effect of clonidine was attenuated by anticholin-
ergic agents. We previously reported that physostigmine
reversed tactile allodynia in a dose-dependent way in rats
but had no effect on the paw flick test, indicating a
differential effect of acetylcholine in heat nociception
and mechanical allodynia in the spinal nerve ligation
model.

Sedation is a major adverse effect caused by most of
the present α2-adrenergic agonists. Because of the po-
tent sedative effect, dexmedetomidine has recently been
approved by the Food and Drug Administration for use
in the sedation of patients in the intensive care unit.
The locus coeruleus (LC) is likely to have an important
contribution to the sedative effects induced by α2-adre-
ergic agonists. Activation of α2 adrenoceptors in the
LC hyperpolarizes cell bodies in the LC. Suppression of
LC neurons is known to be connected with a decrease in
vigilance. Sedation after spinal administration of α2-
adrenergic agonists is considered to reflect supraspinal
redistribution of the spinaly delivered agent.

Sedation was assessed as reduction of spontaneous
locomotor activity in a motility box where the animals
could move freely. Hypolocomotion can be caused by
decreased vigilance and sedation or motor impairment.
High doses α2-adrenergic agonists have been reported to
produce hind limb motor weakness and sedation. However,
no motor impairment was detected in the present
study. In addition, no motor impairment was detected
after intrathecal dexmedetomidine (4.05 µg) in the rota
rod test. When the animals were put into the motility
boxes, they initially showed much spontaneous locomotor
activity when exploring the novel environment for
approximately 15–20 min, and thereafter settled down.

After dexmedetomidine administration, the animals
showed significantly less spontaneous locomotor activity
compared with after radolmidine administration. This
was observed at all doses tested. Even after intrathecal
administration of dexmedetomidine, it has been difficult
to find a therapeutic window dissociating the analgesic
effect from the sedative one. The present results sug-
Fig. 4. The effects of radolmidine and dexmedetomidine on
spontaneous locomotion. As an example of the decrease in
locomotion, the mean (SEM) number of activity counts in the
motility box after intrathecal administration of radolmidine
5 µg (filled circles), dexmedetomidine 5 µg (open squares), or
saline 10 µl (open circles) is shown (A). The dose–response
curves for radolmidine (filled circles) and dexmedetomidine
(open squares) plotting mean percentage of inhibition of activ-
ity, as compared with the locomotor activity in the saline con-
trol group (SEM) 0–15 min after intrathecal administration of
the drugs, are shown (B). The asterisks indicate statistically
significant difference between the drugs.

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tions is also supported by Xu et al., who showed that the sedative effects of dexmedetomidine were less dependent on the exact injection site in the brainstem compared with radolmidine that had to be injected exactly into the LC to produce sedation. Other differences between the molecules may also play a role, as 3 μg dexmedetomidine in the LC produces a highly significant suppression of locomotor activity, whereas radolmidine produced a significant suppression of locomotor activity only at the 10-μg dose.

Hemodynamic effects of intrathecal radolmidine were not assessed in the present study. Eisenach et al. recently showed that in doses up to three times the antinociceptive ED$_{50}$, radolmidine did not decrease arterial blood pressure or heart rate in the sheep, and the hemodynamic effects of radolmidine were significantly less compared with those of clonidine. Direct comparisons of the hemodynamic effects of dexmedetomidine and radolmidine have not been published. The indirect evidence from studies in sheep would indicate that the hemodynamic effects of radolmidine are less compared with those of dexmedetomidine.

In summary, radolmidine has an equipotent antinociceptive effect compared with dexmedetomidine, both against acute noxious heat, and inflammation-induced heat hyperalgesia and mechanical allodynia. Radolmidine and dexmedetomidine also show equipotent antiallodynic effects in the spinal nerve ligation model of neuropathic pain. Radolmidine produces both less hemodynamic and sedative effects than dexmedetomidine in laboratory animals. If these differences can be shown to be of clinical relevance, radolmidine may be a useful spinal analgesic in humans.

References


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