Effect of Systemic Medetomidine, an Alpha2 Adrenoceptor Agonist, on Experimental Pain in Humans

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The effect of systemic (intravenous) medetomidine, an alpha-2 adrenoceptor agonist, on pain thresholds was studied in healthy human subjects (n = 6). Medetomidine produced a dose-dependent (cumulative doses: 25 and 50 μg) sedative effect evaluated by visual analog scale. Also, a dose-dependent decrease of blood pressure but not of heart rate was seen after administration of medetomidine. Pain threshold to electric stimulation of the tooth pulp and cutaneous heat pain threshold were uninfluenced by medetomidine. An index of cutaneous thermal sensitivity to innocuous stimuli, the width of the thermoneural zone, also was uninfluenced by medetomidine. Medetomidine produced a significant attenuation of the affective-motivational component (unpleasantness) of tourniquet-induced ischemic pain, whereas the sensory-discriminative component (pain magnitude estimate) of the ischemic pain was not attenuated. The results suggest that systemic medetomidine alone at subanesthetic but sedative and hypotensive doses does not significantly influence the intensity and thresholds of experimental pain, whereas the affective-motivational component of pain can be attenuated. (Key words: Analgesia, pain: experimental sympathetic nervous system. Alpha-2 adrenergic receptors: medetomidine.)

Many previous studies in animals indicate that systemic administration of clonidine, an alpha-2 adrenoceptor agonist, produces analgesia1-3 resulting from alpha-2 adrenergic mechanisms.4,5 Electrophysiologic studies in animals have shown that systemic clonidine can suppress reflex and sensory neuronal responses to nociceptive stimulation.6,7 Similarly, systemic tizanidine, another alpha-2 adrenoceptor agonist, produces suppression of nociceptive reflex and sensory neuronal responses.6,8 Only a few reports on the pain-alleviating effects of systemic clonidine in humans have been published. In a study on experimental pain, it was shown that systemic clonidine at a sedative and hypotensive dose (2 μg/kg) lacked analgesic effect as determined by electrical stimulation of the skin.10 Two anecdotal case reports have described the analgesic effect of systemic clonidine in a patient with diffuse musculoskeletal pain11 and carcinoma.12 In two studies on postoperative pain in humans, systemic clonidine at a dose of either 2 μg/kg or 200 μg per patient produced a significant analgesic effect.13,14 However, clonidine at a low dose (100 μg per patient) unexpectedly provided less analgesia than placebo in postoperative patients.14 In postherpetic neuralgia, single oral doses of clonidine (200 μg per patient) produced more pain relief than codeine, ibuprofen, or placebo.15 Thus, the few studies on humans reported so far suggest that systemic alpha-2 adrenoceptor agonists may provide a useful treatment for some pain conditions. Additionally, clonidine has been shown to provide analgesia when administered intrathecally and epidurally in humans.16-18

Medetomidine is a new, highly selective and potent alpha-2 adrenoceptor agonist.19,20 Systemically administered dexmedetomidine, a stereoisomer of medetomidine, has been shown to potentiate the anesthetic effects of halothane as assessed by prolonged behavioral response latencies to mechanical pinch in rats.21 However, in awake rats medetomidine at sedative but subanesthetic doses (≤100 μg/kg) suppressed only highly organized pain-related behavior (formalin test), whereas spinally organized pain behavior (tail flick test) was not influenced at subanesthetic doses.22

In the current study we wanted to determine whether systemic medetomidine influences experimental pain in healthy human subjects. Because different submodalities of pain are mediated by different subpopulations of nociceptive neurons that may be differentially influenced by analgesic agents,23 we tested the medetomidine effect on three types of pain: dental pain threshold sensations mediated by intrapulpal A-δ fibers,24,25 cutaneous heat pain mediated by unmyelinated C-fibers,26,27 and tourniquet-induced ischemic pain mediated by deeply located nociceptors.28 Furthermore, two important components of pain sensation, sensory-discriminative and affective-motivational component,29 have been shown to display differential sensitivities to sedative and analgesic drugs.30-32 Therefore, the effect of medetomidine on these two pain components in the ischemic pain test was tested separately.

Materials and Methods

Six healthy human subjects volunteered for the experiment. They were medical school graduates or students,

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all men, and the age range was 21–36 yr. Informed consent was obtained before the experiments. The work was performed according to the institutional protocol of the Department of Physiology, University of Helsinki.

Dental pain thresholds were determined with a constant current stimulator.35 The cathode was glued to an intact upper incisor and surrounded with dental cement to prevent current leakage to gingiva. The anode was attached to the subject's arm. The resistance between the electrodes was monitored throughout the experiment to ensure lack of current leakage. In testing dental pain sensitivity, the pain threshold was determined by slowly increasing the current until the subject felt pain. The test current consisted of constant current pulses of 10-ms duration delivered at a frequency of 5 Hz. Each threshold determination consisted of six separate measurements. At threshold levels dental pain produced by electric stimulation should be mediated by peripheral nerve fibers having conduction velocities in the A-δ range.24,25

Cutaneous thermal sensitivity and heat pain thresholds were determined by a thermostimulator34 composed of Peltier elements with a stimulating surface of 11.8 cm². A thermocouple was attached to the stimulating surface to record the stimulus temperature during the test. The rate of temperature change was 2.2°C per second. Thermal stimuli were applied to the hairy skin of the forearm, and the test site was marked in ink to ensure that the same site was stimulated in each threshold measurement. The adapting skin temperature in the surrounding skin was recorded continuously by a thermoelectrode (Oili 55556 Thermometer, Kone, Inc., Helsinki, Finland), which was located approximately 5 cm from the thermostimulator. In determination of the cutaneous thermal sensitivity, the thermoneutral zone (the interval between warm and cool thresholds) was determined first as described earlier.34 The heat pain threshold was measured after the determination of the interval between the warm and cool thresholds. To avoid skin sensitization, the stimulus temperature was allowed to ascend from the thermoneutral range to the heat pain threshold only three times at 1-min intervals in each threshold determination. Cool sensation should be mediated by specific cold-sensitive A-δ fibers, warmth by specific warmth-sensitive C-fibers, and heat pain threshold sensation with the currently used method by nociceptive C-fibers.26,27 It should be remembered that, although warm and cool thresholds are dependent on the adapting skin temperature, the interval between the cool and warm thresholds and also the heat pain thresholds are not sensitive to changes in the adapting skin temperature.35,36

Ischemic pain was provided by a modification of the submaximal effort tourniquet test described earlier.37 A cuff was placed just proximal to the cubital fossa and inflated to 200 mmHg. Immediately after the start of the cuff inflation, each subject performed five to eight (depending on the subject) repetitions of a controlled exercise. After 10 min of ischemia, the subject was presented with a visual analog scale for evaluation of the pain intensity. The subject was presented with another visual analog scale separately for evaluation of the unpleasantness produced by the ischemia.

The effect of medetomidine (purchased from the Farmos Group Ltd., Turku, Finland) was studied in a double-blind, cross-over fashion. The interval between the medetomidine and the saline day varied from 2 days to 1 week. Each subject was tested at the same time of day (between 9:30 and 11:30 A.M. or 1:30 and 3:30 P.M.). At the beginning of the experiment, an intravenous catheter was inserted for the administration of medetomidine–saline. About 10 min later the subject was presented with a visual analog scale for subjective assessment of vigilance (scale: fully alert to very sleepy). Then, blood pressure, heart rate, and skin temperature were recorded. Next, dental pain thresholds, cutaneous heat pain thresholds, and the index of skin sensitivity to innocuous thermal stimulation (the interval between warm and cool thresholds) were determined as described above.

Medetomidine–saline was given in two doses. The first medetomidine dose was 25 μg. Vigilance, blood pressure, heart rate, skin temperature, and dental pain threshold were determined 10 min after the administration of the first dose of medetomidine–saline. (These measurements could be performed within 5–7 min.) The second dose of medetomidine was also 25 μg (cumulative dose: 50 μg), and it was given 15–20 min after the first dose. Again, vigilance, blood pressure, heart rate, skin temperature, and dental pain threshold were determined 10 min after the second dose. Moreover, cutaneous thermal sensitivity testing and the submaximal effort tourniquet test were performed as described above. Wilcoxon's matched-pairs, signed-rank test was used in statistical evaluation of the data. P < 0.05 was considered to represent a significant difference.

Results

Medetomidine produced a dose-dependent sedative effect as revealed by subjective assessment of alertness (fig. 1). The sedative effect was significant after the dose of 25 μg. After saline administration, no change in vigilance was seen. Medetomidine also produced a dose-dependent decrease of both the systolic and diastolic blood pressure (fig. 1). However, heart rate and skin temperature changes during the experiment were not significant with medetomidine (fig. 2).

The interval between the warm and cool thresholds (an index of cutaneous thermal sensitivity to innocuous stimulation that is independent of the changes in skin
FIG. 1. Dose-dependent decrease of alertness and blood pressure caused by medetomidine. PRE = predrug control; PD1 = 10 min after the administration of the first dose of medetomidine (25 µg)-saline; PD2 = 10 min after the administration of the second dose of medetomidine (25 µg)-saline. Circles = medetomidine condition; squares = saline condition. In the alertness graph, 100% = estimated alertness at the beginning of the experiment in each day. In the blood pressure graph, the upper curves show systolic and the lower curves diastolic blood pressure values. The error bars represent SEM (n = 6). Asterisks indicate significant difference from the corresponding predrug values (*P < 0.05; **P < 0.01; Wilcoxon’s test).

temperature) was not significantly changed after administration of medetomidine (fig. 3). Also, heat pain thresholds were uninfluenced by medetomidine (50 µg; fig. 3). Dental pain thresholds remained at control levels after administration of medetomidine (fig. 4).

The pain intensity estimates of tourniquet-induced ischemic pain were not attenuated after administration of 50 µg of medetomidine when compared with the pain intensity ratings obtained in the saline condition (fig. 4). However, medetomidine significantly attenuated the assessment of unpleasantness produced by ischemia (P < 0.05 compared to the corresponding value in the saline condition; fig. 4).

Discussion

The methods used for determination of cutaneous sensory thresholds in the current study have previously proved adequate in demonstrating the load-dependent elevation of dental pain thresholds and decrease of cutaneous thermal sensitivity to innocuous stimuli during cycle-ergometer exercise, and also dexamethasone-induced attenuation of exercise-induced dental analgesia. Similarly, dental pain thresholds have been shown to rise with increasing amplitude of a conditioning vibrotactile stimulus or with increasing duration of concurrent ischemic pain. Other investigators have demonstrated that pain sensitivity to electric stimulation of the tooth pulp or cutaneous heat pain sensitivity determined with a contact stimulator are affected by opioids (fentanyl). In our previous studies cited above, a group of six subjects has proved to be a large enough sample to produce significant positive results. Thus, the present negative results on the effect of medetomidine on dental and cutaneous heat pain thresholds have been demonstrated with a method that has previously proved sensitive to various

FIG. 2. Lack of significant change in the heart rate or skin temperature by medetomidine. For details and abbreviations see the legend for figure 1.
types of modulatory stimuli with the same number of subjects. The lack of analgesic effect on the sensory-discriminative component of ischemic pain is significant because the affective-motivational component of ischemic pain was attenuated in the same subjects.

The results of the current study are consistent with the previously demonstrated sedative and hypotensive effects in humans after the systemic administration of comparable doses of medetomidine. During the time window used in the current study (10–15 min after the injection), the effect of medetomidine on heart rate was nonsignificant, which is consistent with previous results. Dental pain thresholds and cutaneous thermal sensitivity to innocuous or noxious stimuli were not significantly influenced by medetomidine at sedative and hypotensive doses. The sensory-discriminative component of experimental ischemic pain (pain intensity rating) was not influenced by medetomidine, whereas the affective-motivational component of ischemic pain (unpleasantness) was significantly attenuated by the medetomidine dose of 50 μg.

The analgesic effect of medetomidine at the currently used doses differs from that of opioid analgesics (fentanyl), which predominantly suppress the sensory intensity of pain, although a concomitant reduction of affective pain component has also been reported. Hypnotic drugs such as diazepam are reported to have a predominant effect on the affective-motivational component of pain with little influence on sensory intensity. This effect resembling the effect of medetomidine in the current study. It has been proposed that at the spinal cord level the affective and

![Graph Image](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931345/)
sensory pain components share common relay neurons. According to this hypothesis, the predominant effect of medetomidine on the affective pain component indicates a supraspinal mechanism. However, the parallel processing of affective and sensory pain component already at the spinal cord level has not yet been definitely excluded.

The results of a recent behavioral animal study indicated that in awake rats systemic medetomidine at sedative but subanesthetic doses predominantly attenuated formalin-induced tonic pain component, whereas the phasic formalin-induced pain component was less sensitive to medetomidine. Tail-pinch−induced biting response and spinally organized heat-induced tail flick were uninfluenced by subanesthetic doses of medetomidine. Because in the current human study only the affective-motivational component of ischemic pain was attenuated by medetomidine, it seems that the results on the tonic component of the formalin-induced pain behavior in rats reflect the affective-motivational component of pain.

Concerning the clinical implications of the current experimental pain study, it should be recognized that the interpretations from experimental pain to clinical pain should be made cautiously. With this reservation in mind, the clinical implications of the current study are that the systemic use of a highly selective alpha-2 adrenoceptor agonist may not produce analgesia from pain elicited by the activation of peripheral nociceptors (as experimental pain in the current study) at doses that are clinically applicable without considerable side effects (hypotension, sedation). However, it should be remembered that the results obtained on pain elicited by the activation of peripheral nociceptors (nociceptive pain) may not be applicable to conditions in which pain is elicited by neuropathic mechanisms.

It is noteworthy that single oral clonidine doses have proven effective in postherpetic neuralgia. Thus, additional studies on the effect of alpha-2 adrenoceptor agonists on neuropathic pain are needed, especially because neuropathic pain is reported to be relatively unresponsive to opioids. Clinically, clonidine has also proved effective in the treatment of postoperative pain. Furthermore, it remains to be shown whether medetomidine at higher than currently used doses would produce less depression of blood pressure but clear analgesia. If the emotional component of pain is more of a problem than the intensity of pain, then systemic medetomidine at the currently used doses might also be of help in managing nociceptive pain. Finally, because animal studies have indicated that medetomidine can strongly potentiate the analgesic effect of general anesthetics even at low doses, additional human studies are needed to determine whether systemic medetomidine is a useful analgesic when combined with other anesthetics.

References


