Remifentanil inhibits muscular more than cutaneous pain in humans

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In experimental studies, drug-induced analgesia is usually assessed by cutaneous stimulation. If analgesics act differently on cutaneous and deep nociception, the results of these studies may not be entirely applicable to clinical pain involving deep structures. We tested the hypothesis that opioids have different abilities to inhibit cutaneous and muscular pain. Either the opioid remifentanil or placebo was infused in 12 healthy volunteers in a cross-over fashion. Repeated electrical stimulation (five impulses at 2 Hz) was applied to both skin and muscle. Pain thresholds were recorded. Remifentanil caused a higher increase in the muscular pain thresholds than in the cutaneous pain thresholds ($P=0.035$). We conclude that opioids inhibit muscular pain more strongly than cutaneous pain in humans.

In experimental human studies, the analgesic effect of drugs is usually assessed by applying nociceptive stimuli to the skin.[1] However, in most clinical pain conditions, pain also arises from deep structures. If analgesics act differently on cutaneous and deep nociception, the results of studies exploring only cutaneous pain may not be entirely applicable to clinical pain involving deep structures. Recently, a model for inducing muscle pain by electrical stimulation has been developed.[2] So far, no human study has compared the effects of an analgesic on cutaneous and muscular pain.

In this randomized, placebo-controlled, crossover study on healthy volunteers, we compared the effects of the opioid μ-agonist remifentanil on cutaneous and muscular pain.

Methods

The study was approved by the local ethics committee. The exclusion criteria were pregnancy, hypersensitivity to opioids, the use of any analgesic drug during the last 2 weeks, drug or alcohol abuse, and a history of the use of psychotropic drugs. Twelve healthy volunteers (five females) were enrolled after they had given written informed consent. Their age was 23.8 (21–31) yr and the body weight 70 (SD 9) kg.

Medication

Each volunteer was tested in two sessions at the same time of the day, with an interval of at least 4 days. In each session, either remifentanil or saline 0.9% was administered in a randomized, double-blind fashion. Remifentanil or saline was administered as a computer-controlled intravenous infusion using a Harvard 22 infusion pump (Harvard Apparatus, Edenbridge, Kent, UK). The pump was driven by the software Stanpump (S. Schafer, Palo Alto, CA, USA), which attempts to reach and maintain constant target plasma concentrations. Minto's pharmacokinetic values[3] were used. Plasma concentrations of remifentanil of 1 and 2 ng ml^{-1} were targeted stepwise, even when the syringe contained saline. These concentrations were chosen because they are below the ranges used previously for conscious sedation.[4]

General procedure

All the experiments were performed by the same investigator. For each volunteer, all the tests were applied to the same side of the body (selected randomly) in both the remifentanil and the placebo session. Baseline recordings (0 target plasma concentration) were preceded by a training

session to make the volunteer familiar and comfortable with the testing procedure. The test series at 1 and 2 ng ml^{-1} were performed 10 min after the target concentration of remifentanil had been changed. Immediately before each test series, sedation was assessed using a 10 cm visual analogue scale (0=fully fit, 10=hardly able to keep the eyes open).

Cutaneous stimulation

Two bipolar surface Ag–AgCl electrodes (Dantec, Skovlunde, Denmark) were placed on the skin of the foot, 1 cm distal to the lateral malleolus for elicit cutaneous electrical stimulation.[5] The electrode surface was 7×4 mm and the distance between the two electrodes was 1.5 cm. A train of five square-wave impulses was delivered from a computer-controlled constant current stimulator (University of Aalborg, Aalborg, Denmark). Each of these impulses lasted 1 ms. The duration of the train of five impulses totalled 25 ms, so they were perceived as a single stimulus. This stimulus train was repeated five times at the same intensity, at a frequency of 2 Hz (i.e. every 0.5 s).[5] The current intensity was increased stepwise until the pain threshold was identified. The pain threshold was defined as the minimum stimulus intensity eliciting a subjective increase in perception during the five stimulations, so that the last one or two impulses were perceived as painful. Repeated stimulation was preferred to stimulation with a single electrical stimulus because it has proven more reliable for investigating the analgesic effect of drugs and is not influenced by sedation.[6]

Muscular stimulation

Two 28 G, 3 cm long insulated needle electrodes, with 3 mm long uninsulated tips, were used for the electrical stimulation of muscles (Dantec). The needles were inserted 2 cm into the tibialis anterior muscle, 14 cm distal to the middle of the patella and 2 and 2.5 cm lateral to the lateral edge of the tibia respectively.[2] Because the needle was insulated, concomitant skin stimulation was prevented. Repeated electrical stimulation was performed as described for cutaneous stimulation to determine the pain threshold.

For both cutaneous and muscular stimulation, if the threshold was above a maximal current of 80 mA the threshold was defined as 80 mA. The mean of three threshold determinations was used for the data analysis.

Data analysis

All the data were analysed by the Friedman repeated measures analysis of variance on ranks. The effect of remifentanil on the pain thresholds was analysed by considering the differences between remifentanil and placebo measurements for each individual at each target plasma concentration. To analyse the differential effect on
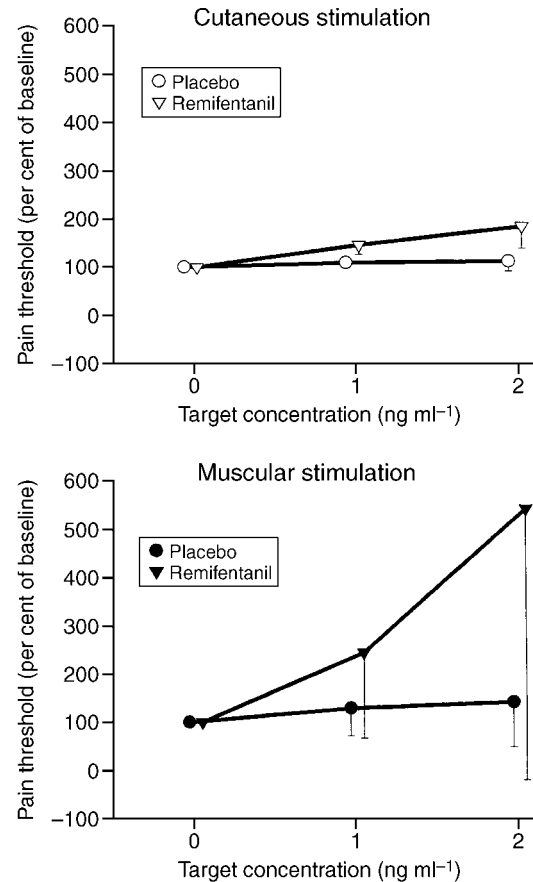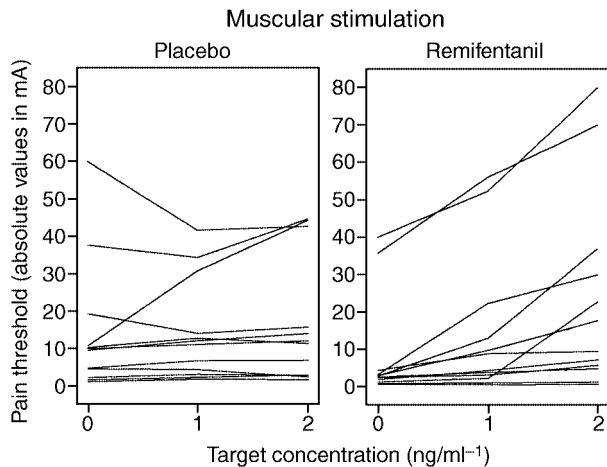

Fig 1 Pain thresholds after repeated electrical stimulation of skin (top) and muscles (bottom). Data (mean and SD) are percentages of baseline recordings. Target concentration 0 represents the baseline recordings, made before starting the infusion pump. In the placebo sessions, the infusion pump was set to reach target plasma concentrations of remifentanil of 1 and 2 ng ml^{-1}, but the syringe contained saline instead of remifentanil. Administration of remifentanil resulted in significantly higher pain thresholds than placebo after both cutaneous ($P<0.001$) and muscular ($P=0.039$) stimulation. Remifentanil caused a higher increase in the thresholds after muscular stimulation than after cutaneous stimulation ($P=0.035$).

cutaneous and muscular stimulation, the differences between muscular and cutaneous thresholds for each subject at each target plasma concentration were considered. This analysis was performed separately for the placebo and the remifentanil sessions. A P value less than 0.05 was considered as significant.

Results

Blinding was frequently incomplete, mostly because of the remifentanil-induced sedation. The mean values of the sedation scores in the remifentanil sessions at target plasma concentrations of 0, 1 and 2 ng ml^{-1} were 1.6 (SD 1.2), 4.5 (2.2) and 6.6 (3.0) respectively. All the subjects were fully cooperative for the experiment.

Muscular stimulation

Fig 2 Pain thresholds for each volunteer after repeated electrical stimulation of muscles. Absolute data are presented.

The results pertaining to the pain thresholds are presented in Fig. 1. Compared with placebo, remifentanil resulted in significantly higher pain thresholds after both cutaneous ($P<0.001$) and muscular ($P=0.039$) stimulation. Placebo affected cutaneous and muscular pain thresholds to the same extent. In contrast, remifentanil caused a higher increase in the thresholds after muscular stimulation than in the thresholds after cutaneous stimulation ($P=0.035$).

Data pertaining to each volunteer for muscular stimulation are presented in Fig. 2.

Discussion

This is the first study comparing the pharmacological modulation of cutaneous and muscular pain in humans. We found that the opioid μ-agonist remifentanil is more effective in inhibiting muscular pain than cutaneous pain.

Animal studies have demonstrated the presence of descending pathways in the spinal cord that are activated by opioidergic supraspinal mechanisms and inhibit the peripheral nociceptive input to spinal cord neurones.[7] These opioidergic mechanisms are much more effective in inhibiting deep than cutaneous nociception.[7]

There is much evidence that analgesics have different actions on responses to different types of nociceptive stimuli, probably because different stimuli evoke different pain mechanisms.[6] [8–10] Depending on the stimulus applied, a drug can vary in efficacy. For instance, propofol increases the threshold of the nociceptive reflex to single stimulation (indicating an analgesic effect), but does not affect the threshold of the nociceptive reflex to repeated stimulation (indicating no analgesic effect) and reduces pain tolerance of mechanical pressure (indicating a hyperalgesic effect).[6] Isoflurane[11] and extradural local anaesthetics[8] [12] more easily inhibit pain induced by single stimuli than pain evoked by repeated stimuli. This is the result of addition of synaptic potentials in the spinal cord neurones during repeated stimulation, which may ultimately lead to an increased neuronal response (temporal summation of nociceptive stimulation).[5] In contrast, NMDA (*N*-methyl-D-aspartate) antagonists strongly decrease pain threshold after repeated nociceptive stimulation but have no effect on pain threshold after a single stimulus.[13] This evidence indicates that the analgesic effect of drugs should be investigated by multimodal testing procedures.[1] Methods investigating the mechanisms involved in clinical pain, such as inflammation,[14] hyperalgesia[15] and temporal[5] and spatial[16] summation, have been used in human studies in an attempt to reduce the gap between experimental and clinical pain.

The new finding of the present study is a further step in the improvement of experimental models. Because analgesics may have different actions on cutaneous and deep pain and because deep pain is involved in most clinical pain conditions, the use of deep pain models is likely to improve the reliability of experimental pain studies. Therefore, the concept of multimodal testing procedure can be extended to the concept of multimodal–multistructure testing, in which nociception arising from different body structures is explored.

In order to apply the same stimulus to skin and muscle, we chose electrical stimulation as the experimental model. Additional methods of inducing muscle pain include the injection of hypertonic saline[17] or algogenic substances, such as bradykinin, serotonin and substance P.[18] [19] Pain thresholds after electrical stimulation of muscles were characterized by wide variability, as shown by the high standard deviations (Fig. 1). This was the result of wide interindividual variability, whereas the response within the experimental session was reproducible for most volunteers (Fig. 2).

In conclusion, we provide evidence for a difference in the abilities of analgesics to affect cutaneous and muscular pain in humans. Muscle stimulation is more effective than cutaneous stimulation in detecting opioid-induced analgesia. These findings, together with the clinical importance of muscle pain, support the wide use of muscle pain models in human studies. The combination of cutaneous and muscular pain models may be a valuable new tool in the preclinical evaluation of analgesics in humans.

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