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Short communication

A brief, high-dose remifentanil infusion partially reverses neuropathic pain in a subgroup of post herpetic neuralgia patients

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ABSTRACT

Mechanism-based therapy for chronic pain is desperately needed. Recent basic science research demonstrated that remifentanil can reverse long-term potentiation at C-fiber synapses in the dorsal horn of rats. In this exploratory, single group study, patients with chronic post-herpetic pain were treated with a single, one-hour, high-dose remifentanil infusion. The mean overall change of pain intensity seven days after treatment was −18 (−7.5; −28.5, 95%CI, $p < 0.001$) points on the numeric rating scale (0–100) (−33 (±11) points amongst responders only). Eleven of 20 patients responded to treatment (≥30% reduction in pain), the mean relative reduction in pain from baseline amongst responders was 61.0%. These promising preliminary results suggest that a mechanism-based reversal of chronic pain may be impending.

1. Introduction

Mechanism-tailored therapy is necessary for effective treatment of chronic pain [1–4]. One hypothesis of chronic pain involves amplification of synaptic strength at C-fiber synapses in the superficial spinal cord dorsal horn [5]. Long-term potentiation (LTP) of synaptic strength is a cellular model for pain amplification at these synapses. Drdla-Schutting and colleagues recently demonstrated that a brief, high-dose, systemic application of the ultra-short acting opioid receptor agonist remifentanil reversed LTP and hyperalgesia in rats [6]. This depotentiation constitutes a previously unrecognized effect of the drug. The aim of the present proof-of-concept study was to transfer these findings for the first time to patients and explore high-dose remifentanil in chronic, post-herpetic (PHN) pain, a condition that might at least partially depend on signal amplification at the spinal level [3,7,8].

2. Methods

Twenty-two PHN patients gave written informed consent for this open-label, single group, exploratory trial. Baseline pain scores (numeric rating scale 0–100) were assessed one day before treatment. On the next day, they received an intravenous, one-hour, target-controlled remifentanil infusion (at 18 $ng^{*}ml^{-1}$) under standard anesthesia care. Pain was assessed one and seven days after treatment. Quantitative Sensory Testing (QST) was used to identify predictors of response (for details [9,10]). Thermal assessments (perception thresholds for cold, cold pain, warmth, and heat pain; tolerance thresholds for heat pain) were made using a Thermal Sensory Analyzer (TSA-2001, Medoc Ltd., ramat-Yishai, Israel). Mechanical pain sensitivity (MPS) and mechanical pain threshold (MPT) were measured with calibrated pin pricks of seven forces 8-512mN (The PinPrick MRC Systems, Heidelberg, Germany). Analyses of pain scores was based on a one-way, repeated-measures ANOVA with Dunnett's tests. Data are presented as mean (±standard deviation) or median and range. The study was approved by the local ethics committee and registered at clinicaltrials.gov (NCT01102101).

3. Results

Data of 20 patients were analyzed (exclusions: one patient did not attend any follow up visit, one refused any further assessments

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Table 1
Pain scores of all patients, and responders and non-responders, at baseline and one and seven days after treatment.

	Baseline NRS	Day 1 NRS	Day 7 NRS	*p*-values
Overall *n = 20*	59 (±16)	42 (±27) (−17.5, −7.1; −27.9)	41 (±25) (−18, −7.5; −28.5)	0.0015 vs. day 1 0.0012 vs. day 7
Responders *n = 11 (55%)*	59 (±13)	27 (±23) (−31.8, −18.5; −45.2)	24 (±16) (−35.0, −25.5; −44.5)	0.0002 vs. day 1 0.0001 vs. day 7
Non-responders *n = 9 (45%)*	62 (±17)	59 (±19) (±2.2, −4,1; ±8.6)	62 (±16) (−0.56, −7.0; 5.9)	n.s.

mean (±standard deviation) and in brackets below mean reductions from baseline and 95% confidence intervals, with *p* values from Dunnett's tests on the right; NRS = numeric rating scale 0–100; n.s. = non-significant ANOVA results with no further testing; responder = ≥30% pain reduction from baseline on day seven after treatment.

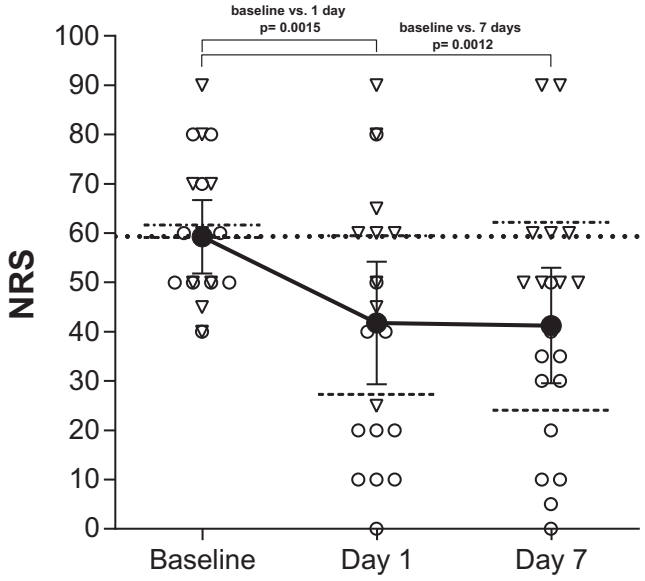

Fig. 1. Pain ratings (NRS, 0–100) at baseline and 1 day and 7 days after treatment; dotted line = baseline pain; black, filled circles: pooled pain ratings (mean, 95%CI); open circles: responders (dashed line = mean); upside-down triangles: non-responders (dot dashed line = mean).

after treatment). Patients (9 male, 11 female) were 69.8 (±11.1) years old and had suffered from PHN a median of 22 months (range 1–312) with an average pain at baseline of 59 (±16). The mean overall change in pain intensity was statistically significant, on average −17.5 (−7.1; −27.9, 95%CI) one day and −18 (−7.5; −28.5) seven days after treatment ($F(2,19) = 13.17$, $p < 0.001$) (see Fig. 1 and Table 1). Of the 20 patients, 11 patients (55%) responded (pain reduction ≥30%) seven days after treatment, of whom 8 (40%) experienced a ≥50% pain reduction. The average change of pain was −61.0% among the responders and +2.2% among non-responders. Responders and non-responders did not differ significantly at baseline concerning age, disease duration, sex distribution, or pain intensity (p for all >0.05). There was weak evidence of non-responders being more hyperalgesic (MPS) than responders at baseline ($p = 0.068$). In the responder group, there was evidence of a significant reduction of MPS ($p = 0.042$) after treatment. We could not identify any predictors of response based on group characteristics or with the use of QST. No serious adverse events occurred.

4. Discussion and conclusion

It has been shown recently that systemic, high-dose remifentanil reverses some forms of LTP at spinal C-fiber synapses as well as mechanical hypersensitivity in rats [6]. Here, we demonstrated that this treatment regimen might be translated to patients. A single, brief, high-dose remifentanil infusion partially and long-lastingly reversed chronic pain in a subgroup of PHN patients.

Currently, treatment of neuropathic pain is lengthy, with high risk of side-effects, and mainly targets symptoms, not causes. This might be the reason for low efficacy and patient satisfaction [11,12]. The reduction of spontaneous pain and mechanical hyperalgesia over one week in our study, well beyond the drug's terminal elimination half-life [13], suggests underlying mechanisms are targeted. Based on the information of this treatment in animals [6], pre-injury conditions might be at least partially restored in humans, possibly constituting a curative treatment effect.

Currently, symptomatic treatment of neuropathic pain achieves a 50% pain reduction in 30–46% of patients [14–16]. In the present study, eight patients (40%) achieved a comparable response. Furthermore, eleven patients (55%) experienced a clinically meaningful reduction of their spontaneous pain. If a "single-shot" treatment achieved similar results to long-term, symptom-directed medication, the benefit for patients would be enormous.

We acknowledge limitations of this exploratory study, such as the small sample size and the lack of a placebo control. Yet, without any prior estimate of the effect in patients, the risk-benefit ratio of a large-scale trial seemed unfavorable. Furthermore, follow-up time was short and no statement can be made about long-term beneficial effects. It is note-worthy that high-dose remifentanil requires standard anesthesia care for patients' safety.

In summary, we provided evidence that a one-time, high-dose treatment with remifentanil significantly reduced pain and hyperalgesia in a proportion of patients suffering from PHN. Our results justify further investigating the effects in a large-scale trial.

Disclosure/Conflict of interest

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