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Title: Effects of a non opioid analgesic on experimental work/effort dyspnea in healthy volunteers: A laser-evoked potential study

Dr. Laurence 10337 Dangers laudangers@gmail.com MD ¹, Dr. Louis 10338 Laviolette louis.laviolette@gmail.com ¹, Dr. Beny 10339 Charbit beny.charbit@psl.aphp.fr MD ², Prof. Dr Thomas 10340 Similowski thomas.similowski@psl.aphp.fr MD ¹ and Dr. Capucine 10434 Morélot-Panzini capucine.morelot@psl.aphp.fr MD ¹. ¹ Pneumologie Et Réanimation Médicale, ER10 UPMC, Groupe Hospitalier Pitié-Salpêtrière, Paris, France, 75651 and ² Centre D'Investigation Clinique Paris EST, UPMC/INSERM UMR S_956, Groupe Hospitalier Pitié-Salpêtrière, Paris, France, 75651 .

Body: Background. Counter-irritation is the attenuation of a painful sensation by a newly occurring heterotopic stimulus that must be noxious in nature. Dyspnea-pain counter-irritation, arising from C-fibers stimulation, has been described with experimental dyspnea of the work/effort type, which inhibits laser evoked cortical potentials (LEPs). Thus, an experimental dyspnea (work/effort) might be relieved by a non-opioid analgesic. Dyspnea-induced counter irritation should then be attenuated, with a lesser degree of LEPs inhibition. Methods. In this randomized, double-blind, placebo-controlled cross-over study, a non opioid analgesic (nefopam) was administrated by intravenous infusion over 30 min to fifteen healthy naïve male subjects, according to power calculations based on available results. The N2P2 component of LEPs was obtained using CO2 laser stimulation on the hand and recorded using EEG. LEPs were acquired during three conditions: spontaneous breathing, spontaneous breathing under nefopam/placebo and experimental dyspnea induced by inspiratory threshold loading under nefopam/placebo. Results. The intensity of experimental dyspnea was not different ($p=0.88$) between nefopam and placebo (VAS rating 3.7 ± 2 cm versus 4 ± 1.9 cm). The amplitude of N2P2 during experimental dyspnea was reduced by $35 \pm 18\%$ and $25 \pm 21\%$ ($\Delta = 37\%$, $p = 0.23$) with placebo and nefopam respectively (power 0.74). Conclusion. There was no statistically significant effect of nefopam on experimental dyspnea and on dyspnea-pain counter-irritation assessed by LEPs, but the study proved underpowered. How interfering with C-fibers function could alleviate dyspnea should be further studied.