Dose dependence of Alfentanil analgesia

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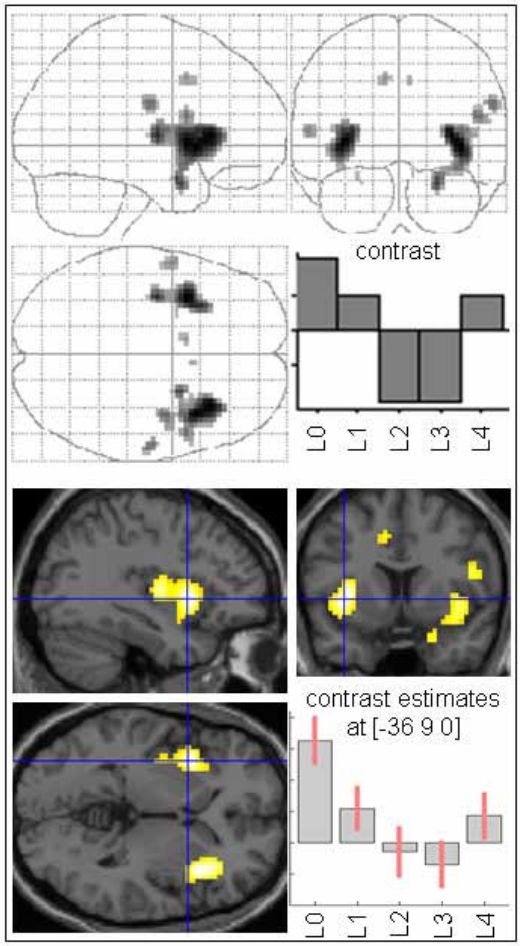
Introduction: The aim of this study was to identify cerebral regions that reflect the dose dependent effects of the opioid alfentanil on painful stimuli and to quantitatively analyze the opioid dose dependent changes in the drug-induced blood-oxygenation level dependent (BOLD) signal changes in healthy volunteers. We anticipated changes in regions associated with the processing of the sensory input signal of pain and in regions associated with the affective response to painful stimulation [1].

Methods: Sixteen healthy volunteers (eight men, eight women, mean age 27.8 ± 4.8 years, range 23.5 to 43.4 years; written informed consent obtained) received a computerized infusion of the μ-opioid receptor agonist alfentanil, at target concentrations of 0, 33.33, 66.67 and 100 ng/ml. Based on information from previous studies, plasma concentrations of alfentanil can be assumed to have completely equilibrated with brain concentrations within 5 min after initiation of each target concentration. Subsequently, at each alfentanil target concentration level and in addition at 20 min after the end of the alfentanil infusion, specific stimulation of nasal nociceptors was achieved by applying painful stimuli of gaseous carbon dioxide (stimulus concentration 65% v/v, duration 300 ms) into the volunteer's right nostril [2, 3]. That is, a total of five stimulus sessions at a duration of each 10 min and with administration of each 23 stimuli at an interval of approximately 30 s were performed at baseline (L0: 0 ng/ml alfentanil), at the three different alfentanil target concentrations (L1: 33.33 ng/ml, L2: 66.67 ng/ml, L3: 100 ng/ml), and finally at 20 min after the infusion was stopped (L4). Subjects were instructed to lay as still as possible and perform an internal rating of pain intensity which was enquired by a visual analogue scale (length 100 mm, left end: "no pain", right end "pain experienced at maximum intensity presented in a training experiment") after completion of the experiment. The BOLD response to these painful stimuli was recorded employing an event-related design on 3.0 T MR head scanner (Siemens Magnetom Allegra) equipped with a 4-channel head coil. Imaging parameters of gradient echo EPI were: parallel imaging method: GRAPPA (R = 2) TE/TR 30 ms/1530 ms, FA 90°, 29 slices, distance factor 40%, matrix size 64x64, voxel size 3x3x3 mm^3. Standard spatial pre-processing and statistical analyses were performed using SPM2 (Wellcome Department of Imaging Neuroscience, London, UK). Single subject analyses (general linear model) resulted in contrast images for each dose level of Alfentanil which were incorporated in a second level ANOVA where the influence of dose was assessed.



Results: Pain related activation in the left and right insular cortex and Rolandic operculum showed a significant ($p < 0.05$, FWE corrected) decrease with increasing alfentanil target concentrations (Fig 1) that showed a tendency to recover after the end of the alfentanil infusion (Fig 1b, inset). At an uncorrected threshold level of $p < 0.001$ an opioid response was also seen in the Cingular cortex and the Amygdala (Fig 1).

Conclusions: The main effects of the specific trigeminal painful stimuli and their modulation by alfentanil were thus seen at areas that belong to the processing circuit of the sensory component of pain. Circuits modulating the affective experience of painful chemo-somatosensory stimuli have also been affected by opioid administration but to a lesser degree than sensory circuits.

References: (1) Oertel et al. Pharmacogenetics 2006; 16: 625-36. **(2)** Lötsch et al. Clin Pharmacol Ther 2005; 78: 278-87. **(3)** Oertel et al. Clin Pharmacol Ther 2006.

Fig 1: Brain areas where pain related activation was significantly ($p < 0.001$ uncorrected) reduced with increasing dose of Alfentanil (L0: 0 ng/ml, L1: 33.33 ng/ml, L2: 66.67 ng/ml, L3: 100 ng/ml, L4: during washout). (a) Glassbrain representation and associated contrast. (b) Sections and contrast estimates at [-36 9 0].