Relation Between Morphine-Induced Analgesia and Changes in Pruriceptive Sensitivity and Superficial Blood Flow: A Randomized, Double-Blind, Placebo-Controlled Trial

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1 Introduction

- It is well known that opioid cause itch as a side effect[1].
- Given that both itch and pain fundamentally rely on signaling along the same C-afferent fiber[2], it is difficult to explain why opioids relieve pain but provoke itch[3].
- Two main hypotheses about opioid induced itch are reported in literature.

1) CNS model: "by a spinal disinhibition mechanism".[4]
2) Peripheral model: "through a cutaneous mast cell-destabilizing effect leading to release of histamine".[5]

2 Aim

The aim of this study was to use oral morphine as a tool to investigate the fundamental mechanisms underlying opioid-induced analgesia and changes in pruriceptive sensitivity in human.

3 Methods

- A total of 24 healthy volunteers (28.0 ± 5.0 years) were enrolled in a randomized, double-blind, placebo-controlled study, and received either oral morphine (20 mg) or identical placebo.
- Three pain threshold modalities (cold, heat, and pressure) were assessed before and 60 minutes after tablets intake.
- Five 4×4 cm square provocation areas were marked: 3 areas on the volar forearms and 2 areas on the mandibular part. The vasomotor reactivity in the marked areas was assessed by full-field laser perfusion imager (FLPI) before and 60 minutes after tablets intake.
- Itch provocations were induced by 1% histamine, cowhage spicules (non-histaminergic itch), or saline (only on the forearm) and the participant rated both the evoked itch and pain intensities for a 10-minutes. Then, the vasomotor response was measured again. All assessment procedures were repeated in all five areas.
- Analysis was conducted by student's t-test, Mann-Whitney U-test, RM-ANOVA and correlation (Pearson or Spearman). A P-value < 0.05 was considered statistically significant for all analyses.
- The regional ethics committee approved the experiment (N-20190049). The study was registered at the ClinicalTrials.gov (NCT04115462).

4 Methods (cont.)

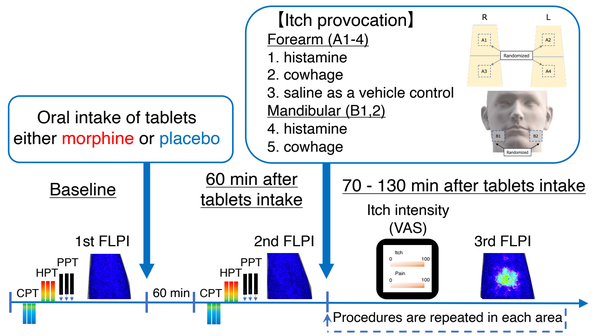

Figure 1. Schema of the study procedures. CPT, cold pain threshold; HPT, heat pain threshold; PPT, pressure pain threshold.

5 Results

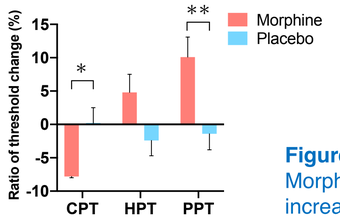

Figure 2. Changes of CPT, HPT, and PPT. Morphine significantly decreased CPT and increased PPT. (*) P < 0.05, (**) P < 0.01.

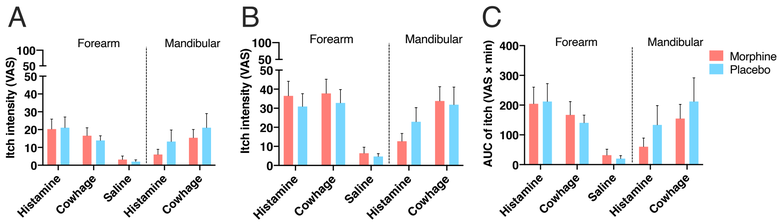

Figure 3. Each itch intensity values following itch provocations on the forearm and mandibular areas. A) Mean value of itch intensity. B) Peak value of itch intensity. C) AUC of itch intensity. There were no significant differences for provoked itch intensity.

6 Results (cont.)

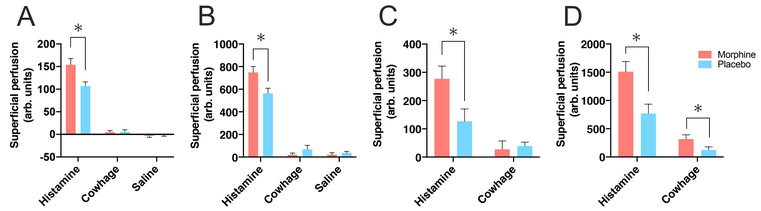

Figure 4. The comparison of superficial blood perfusion following each itch provocations (3rd – 1st FLPI). A) Forearm Mean. B) Forearm Peak. C) Mandibular Mean. D) Mandibular Peak. The superficial blood perfusion following histamine provocation were significantly increased by morphine. (*)P < 0.05.

		Forearm						Mandibular					
		Histamine (VAS)			Cowhage (VAS)			Histamine (VAS)			Cowhage (VAS)		
		Mean	Peak	AUC	Mean	Peak	AUC	Mean	Peak	AUC	Mean	Peak	AUC
ΔCPT	CC	0.05	-0.2	0.05	0.00	-0.10	-0.25	-0.2	-0.05	-0.23	0.13	0.17	0.13
	P value	0.87	0.95	0.87	1.00	0.76	0.44	0.54	0.89	0.48	0.7	0.6	0.7
ΔPPT	CC	0.38	0.28	0.38	0.26	0.09	0.36	0.56	0.42	0.56	0.24	0.26	0.24
	P value	0.22	0.39	0.22	0.42	0.79	0.26	0.06	0.18	0.06	0.45	0.42	0.45

CC: Pearson's or Spearman's correlation coefficient

Table 1. Correlation analysis between itch intensity and pain threshold change. There were no correlations between provoked itch intensity and analgesic efficacy for any of the locations or group.

7 Conclusions

- Oral administration of morphine 20-mg did not affect the itch sensitivity following itch provocations; however, it selectively increased the superficial blood perfusion to histamine provocation on the forearm and mandibular regions compared to placebo by affecting the mast cell destabilizing effect in human (Peripheral model).
- This indicates differences in opioid effect on histaminergic and non-histaminergic evoked itch and that the opioid effect was independent from thermal and mechanical pathways in humans.

References

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