Dose-response relationship after single oral dose administrations of morphine and oxycodone in a human experimental algesimetric model using laser evoked potentials on UV_B-irradiated skin in healthy male subjects

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Introduction

Morphine is a μ-opioid receptor agonist. Its primary therapeutic value is induction of analgesia and sedation and it is the standard against which other opioid analgesics are compared. Oxycodone, a semi-synthetic narcotic and μ- and κ-opioid receptor agonist, is pharmacodynamically comparable to morphine and effective for the relief of moderate to severe pain.

Aim of the study: evaluation of the analgesic efficacy of single oral doses of morphine (MOR) immediate release (IR) 20, 30 and 40 mg and oxycodone (OXY) IR 10, 15 and 20 mg in a human experimental pain model.

The anti-nociceptive/-hyperalgesic efficacy of MOR IR and OXY IR was mainly evaluated and compared to placebo - utilising the method of laser algesimetry[1,2]. A CO_2-Laser was used to induce supra-threshold nociceptive input to determine resulting laser evoked potentials (LEP) from the Vertex-electroencephalogram (EEG). Two main LEP components, N2 and P2 were evaluated by their total peak-to-peak (PtP)-amplitudes. The Laser stimuli were applied to ultraviolet $(UV)_B$-irradiated skin with developing hyperalgesia[3,4,5].

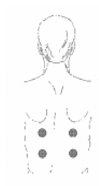
Methods

Subjects, study design and treatments:

Twenty-eight healthy male subjects completed the study. The age ranged between 25 and 51 years and BMI between 22 and 30 kg/m^2. The study was designed as a single-centre, single-dose (SD), double-blind, placebo-controlled, randomized, 7-way intra-individual crossover study. Subjects were randomly assigned to receive one of the following 7 treatments as a single oral dose, *i.e.* MOR IR 20 mg, 30 mg, 40 mg or OXY IR 10 mg, 15 mg, 20 mg or placebo during 7 treatment periods in 1 of 14 treatment sequences. Each treatment was separated by a washout period of at least 7 days, but not more than 14 days.

Induction of inflammation and hyperalgesia:

UV_B-irradiation on skin areas on the back of the subjects (see picture) with 2-fold individual Minimal Erythema Dose (MED) applied 2 hours before medication.



Measurement of anti-nociceptive/-hyperalgesic response:

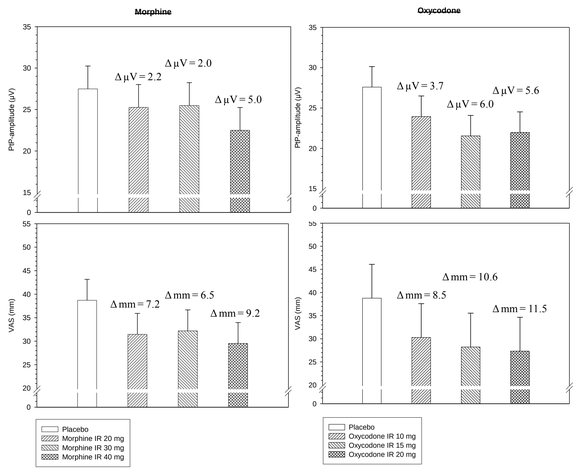
- *Objective algesimetry by LEPs :*
  - On UV_B-irradiated skin.
  - Measurement of total PtP-amplitudes, mean of 12 artifact-free EEG segments.
  - At 0.5, 1, 2, 3, 4, 5 and 6 hours after SD administration.
  - Warm-up session, baseline assessments, wind-up session.
- *Subjective pain impressions by visual analog scale ratings (VAS,100 mm).*

Statistical procedures:

The statistical analysis was based on a linear mixed effects model for the analysis of the repeated measure cross-over design[6]. All analyses were done by the statistical software package SAS Version 9.2. (SAS™, SAS Institute, Cary, NC, USA). Data are shown as (post administration (p.a.)) least squares means with corresponding 95% confidence intervals.

Results

LEP ('PtP-amplitude' p.a.) and VAS ('Post Laser Pain') p.a. on UV_B-irradiated skin



PtP-amplitude :
Effect was significant for MOR IR and OXY IR at all doses - based on differences from placebo (ΔμV) of ≥ 1.25 μV - and considered clinically relevant for MOR IR (40 mg) and OXY IR (all doses) based on ΔμV ≥ 2.5 μV.

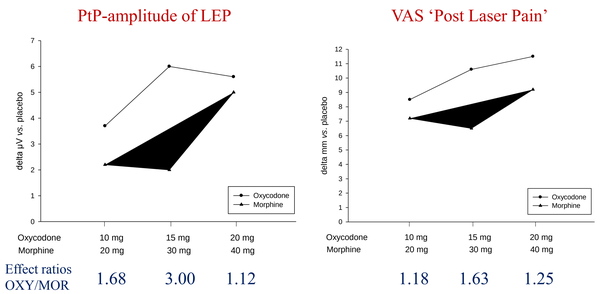
VAS 'Post Laser Pain' :
A reduction, when compared to placebo, between 13 and 18% for MOR IR and between 17 and 23% was seen for OXY IR. A VAS reduction of more than 10% was considered to be clinically relevant.

Hierarchical test procedure and confirmatory results for PtP-amplitude of LEP and VAS 'Post Laser Pain' on UV_B-irradiated skin with p-value adjustment

		Morphine IR			Oxycodone IR		
Hierarchical order	Comparison	p-value LEP (PtP)	p-value VAS	Adjusted p-value both variables	p-value LEP (PtP)	p-value VAS	Adjusted p-value both variables
1	High dose versus Placebo	<0.0001	<0.0001	<0.001	<0.0001	<0.0001	<0.001
2	Linear trend in Placebo-Low-Medium-High dose	0.1119	<0.0001	<0.001	<0.0001	<0.0001	<0.001
3	Medium dose versus Placebo	0.0070	<0.0001	<0.001	<0.0001	<0.0001	<0.001
4	Low dose versus Placebo	0.0023	<0.0001	<0.001	<0.0001	<0.0001	<0.001
5	High dose versus Low dose	0.0001	0.0491	<0.001	0.0066	0.0106	0.0132
6	Medium dose versus Low dose	0.7550	0.4533	ns	0.0008	0.0784	0.0016
7	High dose versus Medium dose	<0.0001	0.0067	ns	0.5457	0.4369	ns

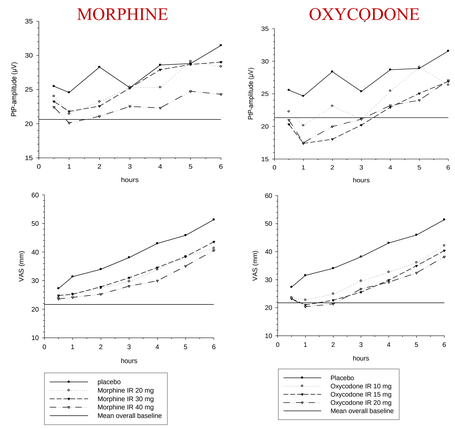
Both MOR IR and OXY IR statistically significantly reduced the PtP-amplitude of LEP or the VAS 'Post-Laser-Pain' on UV_B-irradiated skin compared to placebo at all dose levels. In addition, a statistically significant linear trend was observed.
ns : not significant - due to the hierarchical test procedure.

Effect ratios



The PtP-amplitudes of LEP *vs.* placebo (delta μV) and the VAS *vs.* placebo (delta mm) were higher for OXY IR compared to MOR IR.

Evolution over time of the LEP PtP-amplitude and VAS 'Post Laser Pain' on UV_B-irradiated skin



Hyperalgesia developed over time *vs.* baseline - due to the "acute" exposure to UV_B-irradiation.

Relatively unique time courses of hyperalgesic development were observed with VAS (straight ongoing incline) as compared with LEP (more differentiating).

Principal onset of drug effects of both compounds was around 0.5 hours, with average peak around 1 to 2 hours (less well defined in VAS).

Effect lasting for more than 6 hours for OXY IR (all doses) and MOR IR (40 mg) for LEP and for at least 6 hours for VAS.

Safety and tolerability

There were no clinically relevant safety findings.

Conclusion

MOR IR and OXY IR showed a rapid and persisting anti-nociceptive/anti-hyperalgesic effect in a human experimental algesimetric model.

The anti-nociceptive/anti-hyperalgesic effects of MOR IR and OXY IR were statistically significant vs. placebo and were regarded as clinically relevant.

No major differences in the within-drug effects were seen between the low and the medium doses of MOR IR and between the medium and the high doses of OXY IR, in the LEP as well as in the VAS Pain overall p.a. means.

The effect ratios of OXY IR vs. MOR IR were highest for the medium doses, and lower and comparable for the low and high doses in LEP as well as in VAS Pain.

Time-course, onset and duration of effects revealed differences that were concurrent with the known differences in SD pharmacokinetics of MOR and OXY.

There were no clinically relevant safety findings.

References

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