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Dose-response relationship after single oral dose administrations of morphine and oxycodone using laser-evoked potentials on UVB- and capsaicin-irritated skin in healthy male subjects

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ABSTRACT

The aim of the study was to evaluate the analgesic/antihyperalgesic efficacy and to establish the dose-response relationship of morphine immediate release (IR) and oxycodone IR in a human experimental algesimetric model. Calculated effect ratios for peak-to-peak (PtP) amplitudes of laser-evoked potentials (LEPs) and visual analog scales (VAS) postlaser pain on UVB-irradiated skin (main target variables) were 1.68 and 1.18 respectively for oxycodone 10 mg/morphine 20 mg, 3.00 and 1.63 respectively for oxycodone 15 mg/morphine 30 mg, and 1.12 and 1.25 respectively for oxycodone 20 mg/morphine 40 mg. The effect on the laser-PtP amplitude of morphine at the highest dose (40 mg) and of oxycodone at all doses (10, 15, 20 mg) was considered to be clinically relevant based on a difference from placebo of $\geqslant$2.5 μV. For both compounds, a statistically significant linear trend was observed between dose groups in at least 1 of the 2 main target variables (adjusted *P* value for both end points <.001 at all doses). Hyperalgesia developed over time vs baseline due to acute exposure to UVB irradiation and to topical/occlusive 1% capsaicin solution. For both compounds, the principal onset of analgesic/antihyperalgesic drug effects was around 0.5 hours with an average peak at about 1 to 2 hours and the effect lasting for more than 3 hours (morphine 20 and 30 mg) or 6 hours (morphine 40 mg and oxycodone all doses). In conclusion, the study demonstrated a solid outcome of a mixed objective/subjective human experimental algesimetric model to approach dose-response relationships and analgesic/antihyperalgesic effects of 2 opioids.

1. Introduction

Morphine is the prototype of a narcotic analgesic and the standard against which other opioid analgesics are compared. Morphine is a μ-opioid receptor agonist. Its main effect in the central and peripheral nervous system is activation of μ-opioid receptors. Its primary therapeutic value is induction of analgesia and sedation. However, the analgesia produced by morphine is not primarily caused by a reduction in sensory input, but is also due to sedative/cognitive alterations in the subjective response to painful stimuli [25]. Oxycodone, a semisynthetic narcotic and μ- and κ-opioid receptor agonist, is pharmacodynamically comparable to morphine and effective for the relief of moderate to severe pain. Compared with oral morphine, oral oxycodone has a higher bioavailability and a slightly longer terminal half-life, and is hepatically metabolized by cytochrome P450 [27,28]. Morphine and oxycodone have been marketed for decades and have well-established risk–benefit profiles.

The present study was part of a set of trials aimed at providing information on the dose-response relationship for single opioids. These preparatory trials will help to identify dose(s) to be used in direct head-to-head comparisons of opioids to establish their equianalgesic dose(s). Current equivalence dosing recommendations for opioids generally are based on clinical experience rather than on controlled trials [13]. The optimal approach to investigate equianalgesic doses of opioids would be an intrasubject comparison in patients with acute pain. However, this is not feasible, because acute pain (among others) varies over time and there is no option for an intraindividual crossover. For further evaluation of equianalgesic doses in head-to-head comparisons of opioids, information about linearity/nonlinearity in the dose responses of the

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opioids is essential. The present study was conducted to provide data on single ascending oral doses of morphine IR and oxycodone IR.

The aim of the study was to evaluate the antinociceptive/antihyperalgesic efficacy, as done in previous studies [29,35–38], and the dose-response relationship of morphine IR and oxycodone IR in a human experimental approach utilizing the objective-quantitative (high-resolution) method of laser algesimetry [1,6]. This method is an established and validated alternative to subjective estimation/scoring of patients in clinical models of pain management [9]. A CO_2 laser is used to initiate LEPs, which are recorded from vertex electroencephalogram (EEG). The antinociceptive/antihyperalgesic properties of drugs can be demonstrated objectively and quantitatively by alterations in LEP variables (primarily reductions of amplitudes) vs placebo. The major advantage of this technique of thermal/sensory stimulation with a CO_2 laser is that heat-sensitive ionic channels of polymodal nociceptors of Aδ- (thinly myelinated) and C-fiber (nonmyelinated) types are selectively stimulated/opened [4] without any direct skin contact (the high receptor specificity is also due to the exact skin layer penetration/absorption of far-infrared CO_2 laser stimuli at the level of free nociceptor terminals together with their spectral independency of hemoglobin and melanin content of skin). The LEP signal was evaluated with regard to its complex PtP amplitude as well as to its single N2 and P2 components.

In this study, laser stimuli were applied to sensitized skin (UVB-irradiated/inflamed/sunburned skin [2,17,19,22,24,42] and capsaicin-irritated skin [12,14,15,20,26,30,31,33,35,40,41], using primary/thermosensitive flare area) with developing hyperalgesia as disease-like/"healthy patient" model.

2. Methods

2.1. Study design and treatments

The study was designed as a single-center, single-dose, double-blind, randomized, placebo-controlled, 7-way, intraindividual crossover study. Subjects were randomly assigned to receive one of the following 7 treatments as a single oral dose during 7 treatment periods in 1 of 14 treatment sequences (Williams design [21]): morphine IR (Sevredol, Napp, Cambridge, UK) 20 mg, 30 mg, 40 mg, oxycodone IR (Oxynorm, Napp) 10 mg, 15 mg, 20 mg, and placebo. Each treatment period was separated by a washout of at least 7 days, but not more than 14 days. The doses for morphine and oxycodone were selected in accordance with the study objectives, the experimental character of the study, and the ethical standards of clinical research. Other than reduced tolerability, single doses up to 20 mg oxycodone IR and up to 40 mg morphine IR were not expected to cause significant safety concerns.

Upon arrival at the study center for each treatment period, subjects were fasted for at least 10 hours overnight (fasting compliance was checked by a quick blood sugar test). At least 2 hours after a small standard breakfast, the study medication was administered with 240 mL noncarbonated water. A standard lunch was served not earlier than 4 hours after drug administration (postadministration). Water was allowed until 2 hours before and from 2 hours after administration.

The study protocol was reviewed by the respective local independent ethic committee and by the federal authorities, and was conducted in accordance with the Declaration of Helsinki and its revisions, the Good Clinical Practice guidelines of the International Conference on Harmonisation, and the applicable local laws and regulations. All study participants gave written informed consent before study entry.

2.2. Subjects

Twenty-eight male subjects (mean [SD] age: 35.8 [7.72] years, range: 25 to 51 years; mean [SD] body mass index: 25.2 [1.83] kg/m^2, range: 22 to 30 kg/m^2) participated in the study. Subjects were eligible for participation if they were healthy on the basis of prestudy physical examination, medical history, 12-lead electrocardiogram, vital signs, and clinical laboratory tests performed within 21 days before randomization. Subjects were excluded if they had a history of drug sensitivity or allergy, a recent history of alcohol, drug, or nicotine abuse, widespread acne, scars, or tattoos at the sites of exposure to laser, capsaicin, and UVB, or were otherwise unsuitable for participation in the study. Alcohol, drug, or nicotine abuse was also routinely checked during the study by an acute urine drug abuse panel and by alcohol and carbon monoxide breath tests on the morning of each main assessment day.

Subjects were not allowed to sunbathe or to apply any topical drugs or cosmetics to the sites of exposure to laser, capsaicin, and UVB from 2 weeks before the first administration of study drug until completion of the trial. None of the subjects enrolled reported previous therapies or had concomitant medications administered during the study.

2.3. Induction of inflammation and hyperalgesia

Inflammation and hyperalgesia were induced by means of exposure to UVB irradiation and to capsaicin on skin areas on the backs of the subjects. For predominant UVB irradiation to the respective skin sites, a mixture of peripherally located UVA radiation (6 UVA Philips CLEO 40 W) and centrally positioned UVB radiation (2 UVB Philips TL 20 W/12 tubes) was used. Subjects were exposed to both UVB light and topical capsaicin solution during each treatment period. To avoid a possible change in skin sensitivity as a result of adaptation or overstimulation, skin areas were randomly switched after each treatment period using different dermatomes and contralateral sites.

As part of prestudy assessments, 6 skin areas of approximately 1×1 cm on the back of the subject were exposed to different exposure times of UV irradiation with a predominant UVB part to determine the subject's individual minimum erythema dose. During each treatment period, 1 skin area of approximately 5×5 cm was exposed to UVB (approximately 156 J/m^2) for 2 to 6 minutes with the 2-fold individual minimum erythema dose 2 hours before study drug administration. The individually determined UV dose was kept constant at each main assessment day for each subject. Immediately after the exposure to UVB, 1 contralateral circular skin area of approximately 5.5 cm in diameter (at a higher dermatome) was exposed to a 1% capsaicin solution (INCI: alcoholic *Capsicum frutescens* extract, containing capsaicinoides from *Capsicum annuum annuum*, CAS 84603-55-4). Capsaicin was applied in a topical, occlusive mode for 30 minutes.

2.4. Warm-up session, baseline assessments, and wind-up sessions

An intradiurnal flowchart for the assessments during each treatment period per trial participant is provided in Table 1. To accustom subjects to the study procedures in each of the 7 treatment periods, LEPs were recorded from normal skin at 2 hours 30 minutes before study drug administration (as nonevaluated warm-up). Baseline assessments were made at 2 hours 5 minutes before study drug administration for the UVB-irradiated skin condition (on normal skin) and at 1 hour 25 minutes before study drug administration (after removal of the occlusive capsaicin dressing) for the capsaicin-irritated skin condition. To enhance respectively to maintain the development of hyperalgesia by

Table 1
Intradiurnal flowchart for the assessments during each treatment period per trial participant.

Relative time (h)	PD session	Actions
(-) 3:30		Pass-in fasting; MedCheck: blood sugar fasting; small standard breakfast; alcohol and carbon monoxide breath tests; blood pressure and heart rate; aural temperature; electrocardiogram; urine drug screen; adverse events; co-medication; inclusion/exclusion criteria; clinical chemistry, instrumentation with electrodes
(-) 2:30	Not evaluated	LEP warm-up on normal skin
(-) 2:05	1a	Baseline LEP 1 + VAS 1 (normal skin = baseline for LEP UVB skin)
(-) 2:00		Exposure to 2-fold individual UVB MED (2 to 6 min) and capsaicin* (30 min)
(-) 1:25	1b	Baseline LEP 1 + VAS 1 (capsaicin skin = baseline for capsaicin skin)
(-) 0:30	Not evaluated	LEP wind-up 1 on UVB and capsaicin skin
(-) 0:05	Not evaluated	LEP wind-up 2 on UVB and capsaicin skin
0:00		Study drug administration with 240 mL noncarbonated water
0:30	2	LEP 2 + VAS 2 on UVB and capsaicin skin
1:00	3	LEP 3 + VAS 3 on UVB and capsaicin skin
2:00	4	LEP 4 + VAS 4 on UVB and capsaicin skin
3:00	5	LEP 5 + VAS 5 on UVB and capsaicin skin
4:00	6	LEP 6 + VAS 6 on UVB and capsaicin skin Standard meal
5:00	7	LEP 7 + VAS 7 on UVB and capsaicin skin
6:00	8	LEP 8 + VAS 8 on UVB and capsaicin skin
6:15		Adverse events (final questioning)
	End of main assessment day	

LEP = laser-evoked potential; MED = minimal erythema dose; PD = pharmacodynamic; UVB = ultraviolet B (280 to 320 nm); VAS = visual analog scale.
* Immediately after UVB irradiation (1% capsaicin in alcoholic solution applied in occlusive mode).

repeated nociceptive input (thermal rekindling) [30,31], laser stimuli were additionally applied to UVB-irradiated and to capsaicin-irritated skin at 30 minutes and at 5 minutes before study drug administration (as wind-ups), but were not evaluated. A total of 7 LEP sessions (on normal, UVB-irradiated, and capsaicin-irritated skin) were performed before the dose on each main assessment day. All preadministration and postadministration skin exposure sessions were done in an air-conditioned (laser) laboratory with a temperature setting to 20°C (to stabilize environmental conditions for laser exposure of skin).

2.5. Measurement of antinociceptive/antihyperalgesic response

Quantitative measurement of antinociception/antihyperalgesia was performed using high-resolution laser algesimetry as described elsewhere in more detail [6,35,37]. During each of the 7 treatment periods, LEPs from UVB-irradiated skin and capsaicin-irritated skin were recorded at 30 minutes and 1, 2, 3, 4, 5, and 6 hours after dose (i.e., 7 sessions per day on each skin type), and the nociceptive responses to CO_2 laser pulses were derived from vertex EEG recordings measuring PtP amplitudes of the N2 and P2 components. The CO_2 laser impact stimulus intensity was set above the participant's individual (subjective) nociceptive threshold on normal skin as determined during the prestudy screening assessments. These individual laser intensities remained constant throughout the entire study. The mean of 12 artifact-free, Gaussian phase-free filtered and averaged EEG segments after a laser stimuli of 60-ms (UVB) and 80-ms (capsaicin) pulse duration each was used for evoked potential computing per session. Interstimulus intervals randomly ranged from 4 to 8 seconds in each session to avoid expectancy and the eventual resulting development of habituation/tolerance to laser exposure. The artifact-free state and evaluation of the EEGs (removing/avoiding interferences with eye blinks, myofascial disturbances, relevant acute baseline drifts of EEG signal, etc.) was determined automatically through a fully computerized online program. Because alterations in vigilance are known to have an impact on the amplitudes of evoked potentials [5,8,43], the subjects were loaded and distracted with a pursuit tracking task that was performed for the entire period of each LEP recording. For further vigilance stabilization, distraction of the algesimetric measurement procedure, and to mask external acoustical cues, white noise with a sound pressure of 90 dBA was presented to the subjects. To support the objective-quantitative algesimetric findings in LEPs, the subjective impressions of postlaser pain were rated by the subjects retrospectively via a 100-mm VAS immediately after each LEP session.

2.6. Safety assessments

Throughout the study, safety was monitored by the assessment of adverse events, vital signs (temperature, blood pressure, pulse and respiratory rate), physical examinations, laboratory tests (hematology, biochemistry, and urinalysis), and 12-lead electrocardiograms.

2.7. Statistical procedures

2.7.1. Primary and secondary efficacy variables

A reduction in the complex PtP amplitude has been shown to be a reliable measure of the extent of the antinociceptive/antihyperalgesic drug effects [6,35–40], and the reduction in amplitude correlates well with a reduction in VAS score [6,34,38]. In the present study, the UV model was chosen as the primary model. The UV model is better at mimicking acute/peripheral/inflammatory pain (as found, for example, in posttraumatic and postoperative states) with its cyclooxygenase cascade—being a "real disease," whereas the capsaicin model is closer to mimicking (mixed peripheral/spinal) longer-lasting pain conditions (e.g., pain states with ongoing spinal excitatory nociceptive input). In addition, opiates are known to be more effective in acute pain than in chronic or neuropathic pain states.

The primary efficacy variables in the present study were the PtP amplitude of LEPs and VAS postlaser pain on UVB-irradiated skin at 30 minutes and 1, 2, 3, 4, 5, and 6 hours after the dose. Normal values of the PtP amplitude range between 20 and 30 μV. A reduction of $\geqslant$1.25 μV in PtP amplitude, based on the mean difference vs placebo, was considered significant, and a reduction of $\geqslant$2.5 μV was considered clinically relevant [6, unpublished data]. In clinical settings, a VAS score of 30 mm is regarded to indicate a moderate pain level [7,11].

The secondary efficacy variables were the PtP amplitude of LEPs and the VAS postlaser pain on capsaicin-irritated skin and the single N2 and P2 amplitudes of LEPs on UVB-irradiated skin and on capsaicin-irritated skin at 30 minutes and 1, 2, 3, 4, 5, and 6 hours after the dose. A reduction of $\geqslant$1.25 μV in single component amplitude, based on the mean difference vs placebo, was considered clinically relevant [6, unpublished data].

Effect ratios (oxycodone 10 mg/morphine 20 mg; oxycodone 15 mg/morphine 30 mg; and oxycodone 20 mg/morphine 40 mg) were calculated for PtP amplitudes of LEP and VAS postlaser pain on UVB-irradiated skin.

2.7.2. Sample size determination

Based on previous data [29], a crossover study in a total of 28 subjects would be able to detect a treatment difference at a 2-sided

Table 2
Least-squares means with corresponding 95% confidence intervals for peak-to-peak amplitudes of laser-evoked potential and for visual analog scale postlaser pain on ultraviolet B (280 to 320 nm)–irradiated skin.

Treatment	Peak-to-peak amplitude[†,*] (μV)	Visual analog scale postlaser pain[*] (mm)
Placebo	27.5 (24.7–30.3)	38.7 (34.2–43.2)
Morphine IR 20 mg	25.3 (22.5–28.0)	31.5 (27.0–35.9)
Morphine IR 30 mg	25.5 (22.7–28.2)	32.2 (27.7–36.7)
Morphine IR 40 mg	22.5 (19.7–25.3)	29.5 (25.1–34.0)
Placebo	27.6 (25.0–30.1)	38.8 (31.5–46.1)
Oxycodone IR 10 mg	23.9 (21.4–26.5)	30.3 (23.0–37.6)
Oxycodone IR 15 mg	21.6 (19.0–24.1)	28.2 (20.9–35.5)
Oxycodone IR 20 mg	22.0 (19.4–24.5)	27.3 (20.0–34.6)

IR = immediate release.
[†] A reduction versus placebo of ≥1.25 μV is considered to be significant; A reduction versus placebo of ≥2.5 μV is considered to be clinically relevant.
[*] Data refer to the overall postadministration means (averaged over time).

2.5% significance level with a statistical power of 80%, if the true difference between the treatment groups was 1.75 amplitude units (μV) in LEP. This was based on the assumption that the within-subject standard deviation of the response variable was 5.6.

2.7.3. Statistical model

The statistical analysis of the study was divided for both study agents and was based on a linear mixed-effects model for the analysis of the repeated-measures crossover design [32]. Differences in a single variable between treatment groups were tested by applying the F-test for the contrast of treatment differences obtained from the model. A linear trend test over the dose groups was also performed. The null hypothesis was that for both end points there was no difference. The rejection of the null hypothesis meant that either the PtP amplitude of LEP or the VAS postlaser pain differed between treatment groups. The Bonferroni method was applied for the simultaneous testing of 2 primary efficacy variables. A hierarchical testing procedure was applied to control the experimentwise error rate.

All analyses were done with the statistical software package SAS version 9.2. (SAS, SAS Institute, Cary, NC). Data are shown as overall least-squares means (averaged over time, postadministration) with corresponding 95% confidence intervals (CI).

3. Results

3.1. Primary efficacy variables

3.1.1. LEP (PtP amplitude postadministration) and VAS postlaser pain on UVB-irradiated skin

The PtP amplitude of LEP was reduced compared with placebo by 2.2, 2.0, and 5.0 μV (averaged over time, postadministration) with the 20-, 30-, and 40-mg doses of morphine IR, respectively, and by 3.7, 6.0, and 5.6 μV (averaged over time, postadministration) with the 10-, 15-, and 20-mg doses of oxycodone IR, respectively (Table 2). The effect on the postadministration PtP amplitude of morphine IR at the highest dose (40 mg) and of oxycodone IR at all doses (10, 15, and 20 mg) was considered to be clinically relevant based on a difference from placebo of ⩾2.5 μV.

VAS postlaser pain on UVB-irradiated skin was reduced compared with placebo by 7.2, 6.5, and 9.2 mm (averaged over time) with the 20-, 30-, and 40-mg doses of morphine IR, respectively, and by 8.5, 10.6, and 11.5 mm (averaged over time) with the 10-, 15-, and 20-mg doses of oxycodone IR, respectively (Table 2).

3.1.2. Confirmatory analysis

The hierarchical test procedure and confirmatory results for the primary efficacy variables showed that morphine IR statistically significantly reduced the PtP amplitude of LEPs or the VAS postlaser pain on UVB-irradiated skin compared with placebo at all dose levels. In addition, a statistically significant linear trend was observed (Table 3). The results with morphine IR 40 mg were statistically significantly different from the results with morphine IR 20 mg, but the differences of the high (40 mg) and low (20 mg) dose with the medium dose (30 mg) were not statistically demonstrated.

For oxycodone, a statistically significant difference was observed for all dose levels compared with placebo, as well as a linear trend. The results with oxycodone IR 15 mg and 20 mg were statistically significantly different from the results with oxycodone IR 10 mg, but the difference of the high dose (20 mg) with the medium dose (15 mg) was not statistically demonstrated (Table 3).

3.1.3. Effect ratios

The calculated effect ratios for PtP amplitudes of LEP on UVB-irradiated skin were 1.68 for oxycodone 10 mg/morphine 20 mg,

Table 3
Hierarchical test procedure and confirmatory results for peak-to-peak amplitudes of laser-evoked potential and visual analog scale postlaser pain on ultraviolet B–irradiated skin, adjusted for baseline.

Hierarchical order	Comparison	*P* value laser-evoked potential (peak-to-peak amplitude)	*P* value visual analog scale	Adjusted[*] *P* value, both variables
Morphine IR				
1	High dose vs placebo	<.0001	<.0001	<.001
2	Linear trend in placebo-low-medium-high dose	.1119	<.0001	<.001
3	Medium dose vs placebo	.0070	<.0001	<.001
4	Low dose vs placebo	.0023	<.0001	<.001
5	High dose vs low dose	.0001	.0491	<.001
6	Medium dose vs low dose	.7550	.4533	NS
7	High dose vs medium dose	<.0001	.0067	NS[†]
Oxycodone IR				
1	High dose vs placebo	<.0001	<.0001	<.001
2	Linear trend in placebo-low-medium-high dose	<.0001	<.0001	<.001
3	Medium dose vs placebo	<.0001	<.0001	<.001
4	Low dose vs placebo	<.0001	<.0001	<.001
5	High dose vs low dose	.0066	.0106	.0132
6	Medium dose vs low dose	.0008	.0784	.0016
7	High dose vs medium dose	.5457	.4369	NS

NS = not statistically significant.
[*] p-value adjustment based on the Bonferroni method (a less conservative re-sampling procedure would result in smaller p-values, but not less than the minimum local p-value).
[†] Not significant due to the hierarchical testing procedure.

3.00 for oxycodone 15 mg/morphine 30 mg, and 1.12 for oxycodone 20 mg/morphine 40 mg (Fig. 1). For VAS postlaser pain on UVB-irradiated skin, the ratios were 1.18, 1.63, and 1.25, respectively (Fig. 2). The PtP amplitude differences of LEP vs placebo (delta μV) and the VAS postlaser pain vs placebo (delta mm) were larger for oxycodone IR compared with morphine IR.

3.2. Secondary efficacy variables

3.2.1. LEP (PtP amplitude postadministration) and VAS postlaser pain on capsaicin-irritated skin

On capsaicin-irritated skin, morphine IR at doses of 30 and 40 mg provided a clinically relevant reduction (by ⩾2.5 μV) in the postadministration PtP amplitude of LEP compared with placebo. Oxycodone IR showed a clinically relevant postadministration reduction at all doses (10, 15, and 20 mg) (Table 4).

For VAS postlaser pain on capsaicin-irritated skin, a difference from placebo of 6.6, 3.4, and 8.2 mm (averaged over time) was observed for the 20, 30, and 40 mg doses of morphine IR, respectively, and a difference from placebo of 8.7, 10.8, and 10.7 mm (averaged over time) was observed for the 10, 15, and 20 mg doses of oxycodone IR, respectively (Table 4).

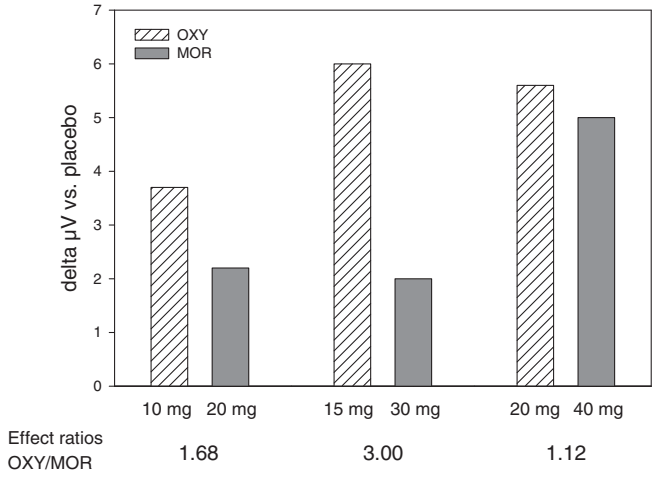

Fig. 1. Peak-to-peak amplitudes of laser-evoked potential vs placebo (delta μV) and effect ratios of oxycodone immediate release vs morphine immediate release on ultraviolet B (280 to 320 nm)–irradiated skin. MOR = morphine; OXY = oxycodone.

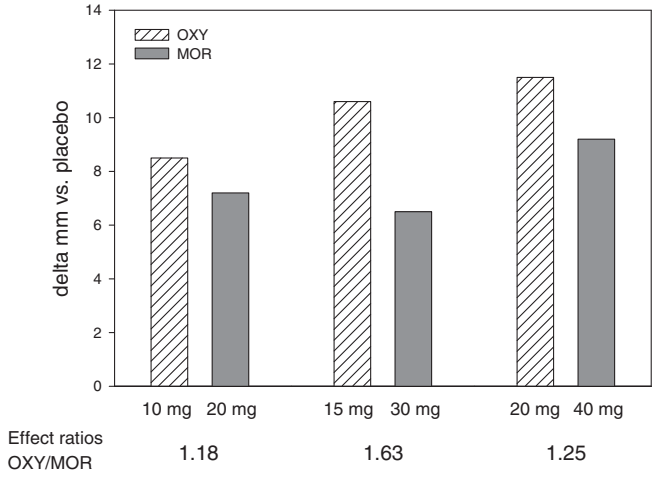

Fig. 2. Visual analog scale postlaser pain vs placebo (delta mm) and effect ratios of oxycodone immediate release vs morphine immediate release on ultraviolet B (280 to 320 nm)–irradiated skin. MOR = morphine; OXY = oxycodone.

Table 4
Least-squares means with corresponding 95% confidence intervals for peak-to-peak amplitudes of laser-evoked potential and for visual analog scale postlaser pain on capsaicin-irritated skin.

Treatment	Peak-to-peak amplitude[†, *] (μV)	Visual analog scale postlaser pain[*] (mm)
Placebo	24.3 (20.5–28.1)	44.8 (40.0–49.7)
Morphine IR 20 mg	22.3 (18.5–26.1)	38.2 (33.3–43.0)
Morphine IR 30 mg	21.8 (18.0–25.6)	41.4 (36.5–46.2)
Morphine IR 40 mg	20.3 (16.5–24.1)	36.6 (31.7–41.5)
Placebo	24.2 (20.3–28.0)	43.9 (36.5–51.2)
Oxycodone IR 10 mg	21.4 (17.6–25.3)	35.2 (27.9–42.6)
Oxycodone IR 15 mg	19.9 (16.1–23.7)	33.1 (25.7–40.4)
Oxycodone IR 20 mg	19.6 (15.8–23.4)	33.2 (25.8–40.5)

IR = immediate release.
[†] A reduction versus placebo of ⩾1.25 μV is considered to be significant; A reduction versus placebo of ⩾2.5 μV is considered to be clinically relevant.
[*] Data refer to the overall postadministration means (averaged over time).

3.2.2. LEP (single N2 and P2 amplitudes) on UVB-irradiated skin

Morphine IR predominantly reduced the single N2 amplitude of LEP on UVB-irradiated skin by at least 1.25 μV at all dose levels (20, 30, and 40 mg) and the single P2 amplitude at the highest dose level (40 mg) when compared with placebo (Table 5). Oxycodone IR reduced both the single N2 and single P2 amplitude of LEPs on UVB-irradiated skin by at least 1.25 μV at all dose levels (10, 15, and 20 mg) when compared with placebo (Table 5).

3.3. Pharmacodynamic effect over time

Both in the UVB-irradiated and the capsaicin-irritated skin model, hyperalgesia developed over time for placebo and for morphine and oxycodone vs the overall mean baseline of normal skin conditions (see the solid, horizontal line in Figs. 3–5). Note that the overall mean baseline was assessed before drug administration on normal skin for UVB irradiation and on capsaicin-irritated skin for capsaicin solution. This was apparent for the objective efficacy variable (LEP) and the subjective efficacy variable (VAS) for UVB- and capsaicin-sensitized skin (Figs. 3–5; VAS data for capsaicin model not shown). The VAS postlaser pain showed a relatively unique time course of hyperalgesic development and end point over the assessment day. In addition, VAS postlaser pain, even under the well-controlled laboratory conditions of the study, showed wider 95% CIs (Table 2) and demonstrated minor interdrug discriminativity and less discriminativity in time efficacy compared with LEPs.

The principal onset of drug effects (values below placebo level) for LEP on UVB-irradiated skin was at around the 30-minute time

Table 5
Least-squares means with corresponding 95% confidence intervals for N2 and P2 amplitudes of laser-evoked potentials on ultraviolet B (280 to 320 nm)–irradiated skin.

Treatment	N2 amplitude (μV)[†, *]	P2 amplitude (μV)[†, *]
Placebo	13.8 (11.9–15.7)	13.8 (11.8–15.8)
Morphine IR 20 mg	12.1 (10.2–14.0)	13.2 (11.1–15.2)
Morphine IR 30 mg	12.4 (10.5–14.3)	13.0 (11.0–15.1)
Morphine IR 40 mg	11.1 (9.2–13.0)	11.4 (9.4–13.5)
Placebo	13.9 (12.0–15.8)	13.7 (11.8–15.6)
Oxycodone IR 10 mg	12.1 (10.1–14.0)	11.9 (10.0–13.8)
Oxycodone IR 15 mg	10.3 (8.4–12.2)	11.2 (9.3–13.1)
Oxycodone IR 20 mg	11.0 (9.1–13.0)	11.0 (9.1–12.8)

IR = immediate release.
[†] A reduction versus placebo of ⩾ 1.25 μV is considered to be significant; A reduction versus placebo of ⩾ 2.5 μV is considered to be clinically relevant.
[*] Data refer to the overall postadministration means (averaged over time).

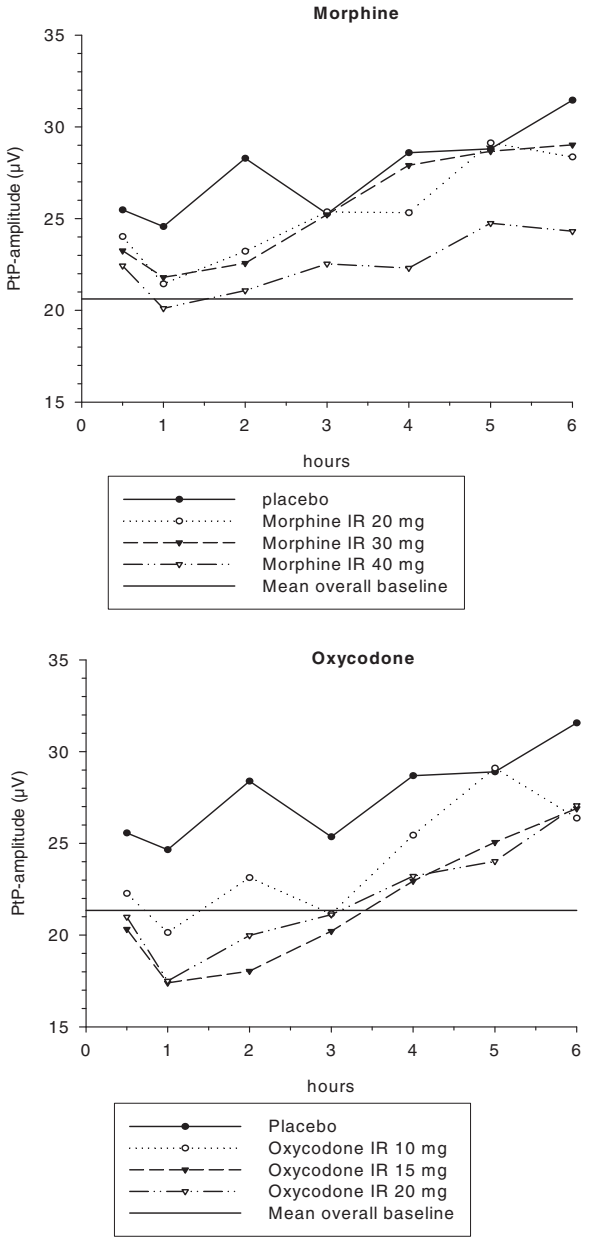

Fig. 3. Evolution over time of the PtP amplitudes of laser-evoked potentials on ultraviolet B (280 to 320 nm)–irradiated skin. Least-squares means of measurements taken from 28 subjects after administration of morphine IR, oxycodone IR, or placebo. IR = immediate release; PtP = peak-to-peak amplitude.

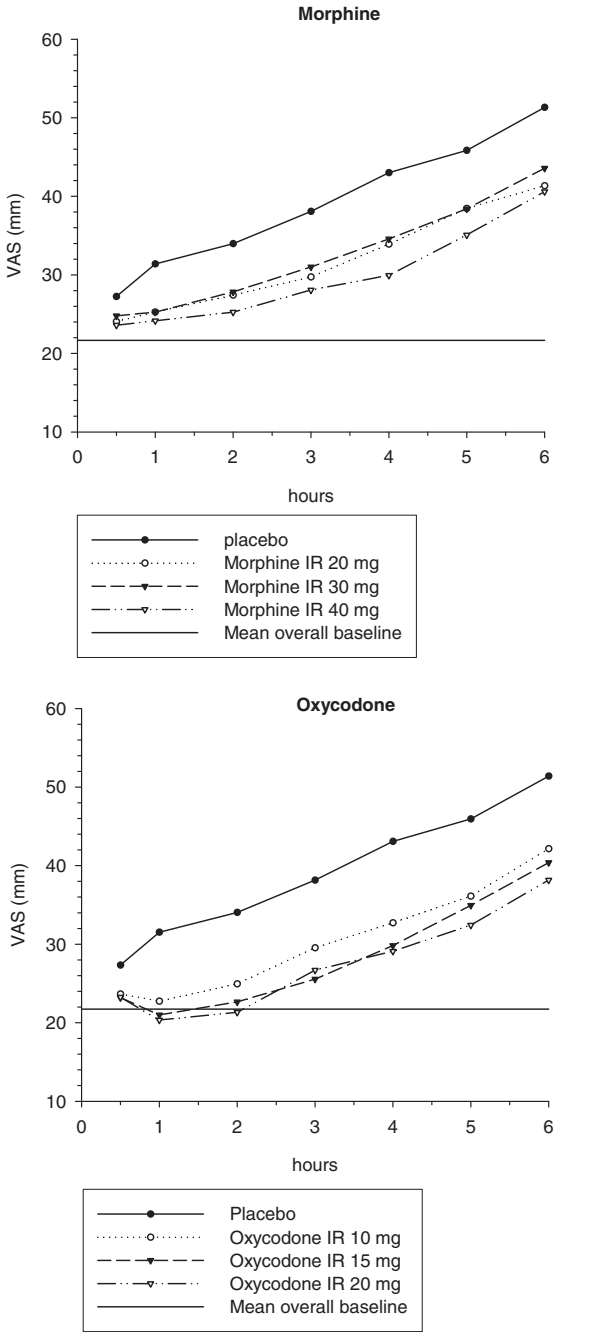

Fig. 4. Evolution over time of VAS postlaser pain on ultraviolet B (280 to 320 nm)–irradiated skin. Least-squares means of measurements taken from 28 subjects after administration of morphine IR, oxycodone IR, or placebo. IR = immediate release; VAS = visual analog scale.

point after morphine IR and oxycodone IR administration. Time to maximum effect (relative to drug intake) for morphine IR and oxycodone IR was about 1 to 2 hours. Positive drug effects for LEPs on UVB-irradiated skin sustained for at least 6 hours with the 40-mg dose of morphine IR and the 10-, 15-, and 20-mg doses of oxycodone IR (Fig. 3). Morphine IR demonstrated a relatively short effect with the 20- and 30-mg doses (about 3 hours).

The principal onset of drug effects for VAS postlaser pain on UVB-irradiated skin was at around the 30-minute time point after morphine IR and oxycodone IR administration. Time to maximum effect for morphine IR and oxycodone IR was less well defined in VAS than for LEPs on UVB-irradiated skin. Positive drug effects for VAS postlaser pain on UVB-irradiated skin were sustained for at least 6 hours (Fig. 4). A similar pattern of results was observed for capsaicin-irritated skin (VAS data not shown).

3.4. Safety and tolerability

All subjects reported 1 or more adverse events. The most commonly reported adverse events (>30%) were dry mouth and a sensation of heaviness (36% each) with morphine IR, and dizziness (66%), somnolence, and hyperhydrosis (34% each) with oxycodone IR. The incidence of adverse events increased with increasing doses. All adverse events were rated as mild or moderate and resolved spontaneously. No clinically significant changes were observed in vital signs, physical examinations, and ECGs. Except for 1 case of (isolated) increased lipase, no other clinically significant changes occurred in laboratory values.

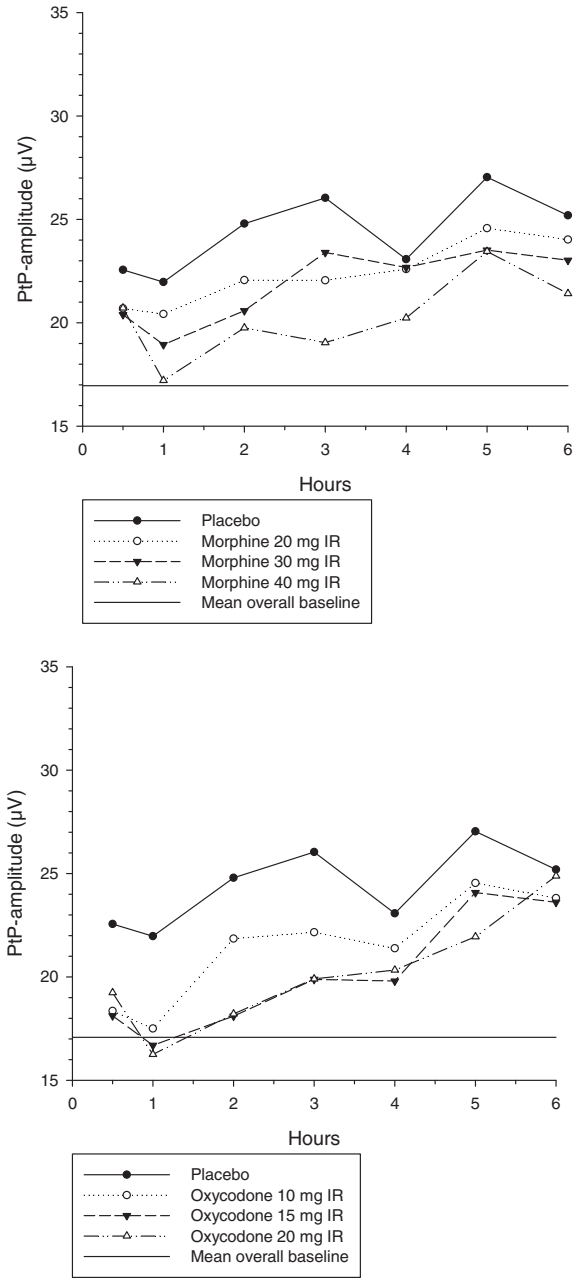

Fig. 5. Evolution over time of the PtP amplitudes of laser-evoked potential on capsaicin-irritated skin. Least-squares means of measurements taken from 28 subjects after administration of morphine IR, oxycodone IR, or placebo. IR = immediate release; PtP = peak-to-peak amplitude.

4. Discussion

Pain is a complex phenomenon consisting of interactions in nociceptive sensory input, psychological factors, and socioenvironmental factors [44]. Evaluations of clinical pain states are difficult due to the patients' sole subjective scoring via analog or categorical scales or pain diaries. These ratings are often confounded by co-medication or by additional pathophysiological, cognitive-, or vigilance-based influences. Therefore, such measures are not very discriminative in detailed algesimetric investigations of peripheral and central nociceptive processing and elucidation of underlying mechanisms [29].

The introduction of validated laser technology in algesimetry has been a great step forward with regard to investigations in human pain processing and is supported by previous and actual statements and guidelines of the European Federation of Neurological Societies [9]. Specific laser stimulations can repeatedly be applied to normal [6,34] and to hyperalgesic/inflamed skin (due to UVB irradiation or capsaicin irritation [6,34–38,40]) to generate LEPs from vertex EEG by triggering, Gaussian phase-free filtering, and averaging of artifact-free EEG responses to contact-free nociceptive stimuli. The antinociceptive and antihyperalgesic properties of drugs can objectively and/or quantitatively be demonstrated by alterations in LEP variables (preferably the amplitudes). Differentiations in nociceptive processing and simulations can especially be made with laser applications using different skin types (normal, UV-irradiated, and capsaicin-irritated skin). LEPs on normal skin are a check on stable intradiurnal perception/processing conditions and/or a check on pure/sole nociceptive compound activity [6,34], a situation that is normally not the case in clinical pain with inflammatory and/or neuropathic or chronic components. LEPs on UVB-irradiated skin primarily mimic acute, posttraumatic, and/or postoperative pain [6,34], whereas LEPs on capsaicin-irritated skin predominantly investigate conditions close to neuropathic pain, due to a longer-lasting nociceptive input on the spinal level [6,30,31,35] (inducing a mixed peripheral-central hyperalgesia), by a reduction of TRPV1 channel opening already at about room temperature, instead of approximately 43°C. Greffrath et al. [16] found that an infrared diode laser evoked typical heat-activated inward currents in cultured rat sensory neurons that were all sensitive to capsaicin. The same laser stimuli evoked pain sensations and LEPs in humans, and the pain threshold was about the same as for eliciting cellular inward currents. However, there are also findings of hypoalgesia in laser stimulation after capsaicin applications [10,46,47], which is in contrast to our results. The topical capsaicin applications in these studies were different with regard to application site, duration, concentration, and galenic preparations, and the capsaicin effects only covered a short interval (up to 1 hour vs up to 6 hours and fostered by the predose and inherent postdose laser radiant-heat kindling of capsaicin-irritated skin in our study).

Also of note is that the applied UV sunburn is not only a model, but a real disease [6] and implies the complete cyclooxygenase cascade as, for example, seen in acute (inflammatory) clinical pain states (posttraumatic and postoperative). The laser allows proof-of-concept in efficacy, onset of efficacy, and time- and dose-dependent efficacy, thereby optimizing and shortening the preparation and reducing the expenses of subsequent extensive clinical and ambulant patient studies. It also allows assessment of adequate and reasonable drug combinations in smaller groups of healthy subjects in ethically acceptable intraindividual crossover designs [6, unpublished data], which are of short duration, part of proof-of-concept approaches, and in go/no-go decisions. Drug classes that have been investigated with the laser model so far include nonsteroidal anti-inflammatory drugs, opioids/opiates, antihistamines, antidepressants, antiepileptics, and others [6].

Reclassification and descriptive confirmation of the detected antinociceptive effect magnitude and its link to clinical relevance were drawn from a meta-analysis, summarizing former studies with known clinically effective standard analgesics (e.g., from nonsteroidal anti-inflammatory drug and opiate type) [3,6, unpublished data]. In clinical settings, a VAS score of 30 mm is considered to indicate a moderate pain level [7,11]. The VAS laser pain rating has been shown to reach clinical dimensions with levels of 50 mm and more at the end of the assessment days (including hyperalgesic development under UVB and capsaicin exposure) [11], which have also been rated in postsurgery pain [7].

The doses of morphine IR and oxycodone IR chosen in this study are adequate for pain reduction in clinical practice, were expected to be reasonably well tolerated in healthy male subjects, and were

assumed to be equianalgesic based on equianalgesic potency tables in the literature [13]. The latter do not allow an easy extrapolation of solid equipotent dose (or dose-response) data due to differences in clinical and experimental paradigms and administration modes. Based on the literature, the analgesic potency ratio between morphine IR and oxycodone IR was expected to be 1:2 [13]. However, the results of the current study suggest that the ratio depends on the applied doses of morphine IR and oxycodone IR.

In both the UVB-irradiated and the capsaicin-irritated skin model, the results obtained with morphine IR and with oxycodone IR were significantly different from placebo at all dose levels in at least 1 of the main target variables, i.e. the PtP amplitude of LEP or VAS postlaser pain on UVB-irradiated skin. For both compounds, a linear, statistically significant trend was observed between dose groups in at least 1 of the main target variables. The effect ratios of oxycodone IR vs morphine IR were highest for the medium doses, and lower and comparable for the low and high doses. This pattern in the effect ratios of oxycodone IR vs morphine IR was observed for both skin conditions, as well as in LEPs and in VAS, confirming a consistency of this phenomenon.

Morphine IR provided a clinically relevant reduction ($\geqslant$1.25 μV) in the single N2 amplitude at all dose levels (20, 30, and 40 mg), whereas a clinically relevant reduction in the P2 amplitude was observed at the highest dose (40 mg) only. The antinociceptive/antihyperalgesic effect of morphine on the N2 amplitude was consistently more pronounced than its effect on the P2 amplitude. This is in line with previous observations with morphine [18,23,45]. For oxycodone IR, the effects on both the N2 and the P2 amplitude were considered to be clinically relevant and were more balanced for both LEP components than with morphine IR.

In both the UVB-irradiated and the capsaicin-irritated skin model, hyperalgesia developed over time vs baseline due to the acute exposure to UVB irradiation and topical capsaicin solution [6,35,38]. This was evident for the objective (LEP) as well as for the subjective (VAS) efficacy variable. The increasing PtP amplitudes and VAS scores in both skin types are due to the ongoing development of inflammation (taking 12 to 24 hours to maximum hyperalgesia) and to the thermal kindling effect of repeated laser shots and sessions, which hit varying skin spots (however always remaining inside the same dermatome per main assessment day), thereby potentially facilitating spinal transmission (spinal sensitization). This acute hyperalgesic incline allows an easier and more differentiated evaluation of antinociceptive/anti-inflammatory drug effects than working on nonsensitized skin or in steady-state skin conditions. A proof that LEP sessions do not possess an inherent hyperalgesic development potency per se is shown by the neutral time courses all over the day in other drug studies, with a simultaneous intradiurnal control of LEPs in normal skin conditions [6,34], remaining at about predose baseline levels. The relatively unique time course of hyperalgesic development—straight ongoing incline in VAS—observed with VAS postlaser pain, as compared with the respective more differentiating time courses in PtP amplitudes of LEPs, implicates important subjective and objective influences as nuisance, cognition, and vigilance factors, e.g. induced by opioidergic mechanisms as vegetative reactions like nausea, vertigo, sweating, sedation, and cognitive shifts [29]. To rely on algesimetric measurements only on subjective pain intensity estimates is therefore debatable [29]. Subjective pain measurements are showing a higher variance in data and are additionally charged by the long measuring days increasing weariness (accumulating from further nonanalgesic, cognitive/sedative drug effects), which as psychological variables do not show up in the LEP PtP amplitudes [6,34]. There is work on significant increases of pain sensitivity ratings in sleepy pain-free normal subjects [5] and in sleep-deprived subjects, who deliver higher subjective pain ratings while their LEP amplitudes remain constant or are even reduced [43].

In conclusion, morphine IR and oxycodone IR showed a rapid and persisting antinociceptive/antihyperalgesic effect in an experimental, objective, and quantitative human algesimetric model. The antinociceptive/antihyperalgesic effects of morphine IR and oxycodone IR, determined by a reduction in nociception-related signals, were statistically significantly evident vs placebo and were regarded as clinically relevant. No major differences in the within-drug effects could be detected between the low and medium doses of morphine IR and between the medium and high doses of oxycodone IR, as consistently seen in the LEPs and in the VAS overall postadministration means. The effect ratios of oxycodone IR vs morphine IR were highest for the medium doses, and lower and comparable for the low and high doses in LEPs and in VAS, confirming a consistency of this dose-dependent phenomenon. The time course, onset of effects, and duration of effects revealed differences that were concurrent with the known differences in single-dose pharmacokinetics of morphine and oxycodone. No clinically relevant or unexpected safety findings were raised during the course of the study.

Conflict of interest statement

There was no potential conflict of interest relationship.

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