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Chapter 5

A randomized controlled trial and novel mathematical analysis of the analgesic effect of oxycodone versus paracetamol orodispersible tablets

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Chapter 5 | A randomized controlled trial and novel mathematical analysis of the analgesic effect of oxycodone versus paracetamol orodispersible tablets

INTRODUCTION

Many patients with chronic cancer and non-cancer pain experience episodes of breakthrough pain, which is defined as “a transitory exacerbation of pain that occurs on a background of otherwise stable pain while using long-term, around-the-clock analgesics to control chronic pain”. Breakthrough pain is usually treated with rapid onset opioid analgesics and a number of formulations using different administration routes are available, including intranasal, sublingual, oral transmucosal and transbuccal routes. For effective treatment of breakthrough pain, or any other form of severe acute pain, a rapid onset of action is important. Most studies that assess the efficacy of rapidly acting opioids in immediate-release formulations use a fixed time-point at which superiority of one treatment over another is assessed (e.g. 15 or 30 min following drug intake) without taking into account the full temporal profile of analgesic effect.

A relatively new treatment option for breakthrough pain is the use of orodispersible (i.e. disintegrating or melt) tablets (OT) of lipophilic opioids that are applied on or under the tongue and that give a rapid onset of analgesia. The OT melts in the mouth but is predominantly absorbed in the gut. Few studies have characterized the onset of analgesia of orodispersible tablets. Rauck et al. showed a significant reduction in pain intensity at 10 min following administration of sublingual orodispersible fentanyl. In the current study we quantified the antinociceptive effect of a 20 mg orodispersible oxycodone tablet (OOT) in a population of healthy volunteers. We recently showed that a longitudinal pharmacodynamic analysis provides important information on the onset and offset of action of analgesic treatment and argued that this approach is superior to analysis of effect at fixed time points during the course of treatment. In the current study we applied a modified pharmacodynamic analysis to overcome some of the problems of the previous analysis using two experimental pain models (electrical and pressure pain) over a 5-hour test period. The effect of OOT was assessed relative to an active placebo comparator, a 500 mg paracetamol orodispersible tablet (POT), using a randomized, double blind and crossover design.

The main aim of the study was to quantify the temporal antinociceptive profile of administration of OOT versus POT. We hypothesize that oxycodone produces greater analgesia than the active comparator and meaningful analgesia, as defined by a 30% increase in response thresholds within 20 min.
METHODS

Subjects
Healthy female volunteers were recruited to participate in the study performed at Leiden University Medical Center after approval of the protocol by the local Medical Ethics Committee. Female volunteers were chosen for reasons of availability and the fact that most drug trials systematically exclude females. The trial was registered (ISRCTN59463510) at controlled-trials.com and recruitment lasted from 1 January, 2013 - 1 March 2013. All participants gave written informed consent and underwent a physical examination before enrollment in the study. Inclusion criteria were: age 18 - 65 years, body mass index 18 - 35 kg/m² and body weight 50 - 100 kg. Exclusion criteria included: (a) a history of mental health problems; (b) a history of alcohol or substance abuse; (c) two or more of alcohol units/day; (d) positive pregnancy test; (e) not using oral contraceptives, not surgically sterilized, or not post-menopausal; (f) a history of allergic or anaphylactic reaction or significant intolerability to prescription or non-prescription drugs or food, and (g) any other condition that in the opinion of the investigator would complicate or compromise the study, or the well-being of the subject.

Study design
In this randomized, double blind, active-comparator, crossover study, subjects were randomized to receive one orodispersible oxycodone 20 mg tablet (OxyNorm Instant, Mundipharma Pharmaceuticals BV, Hoevelaken, The Netherlands) on one occasion and placebo (one paracetamol 500 mg orodispersible tablet; Roter, Hilversum, The Netherlands) on another occasion. One week was allowed for washout. The subjects were requested to fast for at least 6-hours prior to the intake of study medication. The tablets were placed under the tongue; the subject was not allowed to swallow until the drug had completely disintegrated. To assess the analgesic treatment efficacy, electrical and pressure nociceptive assays were applied. Prior to the study the subjects were familiarized with both pain tests.

Electrical noxious stimulation
A locally designed and manufactured transcutaneous electrical stimulation device (TES) was used to create a constant current electrical stimulus train (stimulation at 20 Hz, pulse duration 0.2 ms)\(\textsuperscript{12}\). The device was attached to 2 surface electrodes that were applied on the skin over the tibial bone of the non-dominant side. The location of the electrodes was chosen such that the electrical stimulation did not cause any muscle contraction. The current over the electrodes was increased from 0 mA at a rate of 1 mA/s,
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with a cutoff of 128 mA. The subjects were instructed to indicate when the stimulation became painful (electrical pain threshold, EPTh) by pressing a button on a control box. By pressing a second button the subjects could end the stimulus train when the pain was perceived as intolerable (electrical pain tolerance, EPTol). Prior to drug administration baseline values were obtained. To that end, three tests were performed at 5 min intervals. The three currents obtained for pain threshold and tolerance were averaged and served as baseline values. Following treatment, TES was applied at t = 5, 10, 15, 20, 25, 35, 45, 55, 65, 75, 85, 95, 110, 125, 140, 170 200, 230, 260 and 290 min.

Pressure pain
An FPN 100 N Algometer (FDN 100, Wagner Instruments Inc., Greenwich, CT) was used to deliver pressure pain on an area of 1 cm² between thumb and index finger. The FDN 100 has a force capacity (± accuracy) of 100 ± 2 N (10 ± 0.2 kgf) and graduation of 1 N (100 gf), respectively. A gradually increasing pressure was manually applied and the subjects were asked to indicate when the procedure became painful (pressure pain threshold, PPTh). The pressure was then released. Following treatment, the pressure test was applied at t = 30, 60, 90, 120, 180, 240 and 300 min.

Randomization and blinding
Randomization was performed by the local pharmacy using a computer-generated randomization list. The pharmacy repackaged the tablets into unmarked and identical containers. The repackaged tablets were allocated 1:1 on the morning of the study ensuring blinding of volunteers and investigators.

Conventional statistical analysis
The study was powered to detect a 25% difference in treatment effect on EPTol (SD 25%, power 0.9). To determine the effect of treatment, a two-way analysis of variance was performed (factors treatment, time and treatment x time). Comparisons of time-effects and the area-under-the time-response curves (AUC), determined from the linear trapezoid rule, were compared using t-tests. The statistical analysis was performed with the R statistical package (version 2.8, R-project; www.r-project.org); the comparisons were 2-sided with p-values < 0.05 considered significant.

Pharmacodynamic analysis
A longitudinal pharmacodynamic model was developed to describe the time course of the pain responses of primary end-points EPTol, EPTh and PPT, following administration of oxycodone and paracetamol. The model was constructed with the non-linear mixed
effect modeling software NONMEM version VII (ICON Development Solutions, Elliott City, MD). The pharmacodynamic model consisted of a modified Bateman function that describes the time course of the response in terms of two first-order rate constants describing the waxing (with rate constant $k_{\text{ON}}$) and waning (with rate constant $k_{\text{OFF}}$) of the response. The model is of the form:

$$\text{Effect}(t) = \text{BLN} \cdot [1 + \text{EFF} \cdot \text{BF}(t)] + \text{TRD}/300 \cdot t$$  \hspace{1cm} (A1)

where $t$ is time, BLN is the baseline value of the measured variables (EPTh, EPTol and PPTh), EFF the maximum observed drug effect (effect at $T_{\text{MAX}}$ where $\text{BF}(t = T_{\text{MAX}})$ has a maximum possible value of 1), TRD a trend term and BF the modified Bateman Function with (cf. Martini et al.):

$$\text{BF} = \frac{e^{-k_{\text{OFF}} \cdot t} - e^{-k_{\text{ON}} \cdot t}}{\left(\frac{k_{\text{ON}}}{k_{\text{OFF}}} - k_{\text{OFF}}\right)}$$  \hspace{1cm} (A2)

In case $k_{\text{ON}} = k_{\text{OFF}} = k$, the modified Bateman Function, $\text{BF}(t)$, equals $k \cdot t \cdot e^{(-k \cdot t + 1)}$. The time to maximum effect, $T_{\text{MAX}}$, was calculated as follows:

$$T_{\text{MAX}} = \log\left(k_{\text{ON}}/k_{\text{OFF}}\right)/(k_{\text{ON}} - k_{\text{OFF}}), \text{ when } k_{\text{ON}} \neq k_{\text{OFF}}$$  \hspace{1cm} (A3)

and

$$T_{\text{MAX}} = 1/k, \text{ when } k_{\text{ON}} = k_{\text{OFF}}$$  \hspace{1cm} (A4)

Random effects were included in the model allowing for assessment of between-subject variability ($\omega^2$) and within-subject or residual variability ($\sigma$). Analysis was performed simultaneously on the complete data set allowing discrimination of drug effect on EFF, $k_{\text{ON}}$ and $k_{\text{OFF}}$. $p$-values $< 0.01$ were considered significant. In the analysis the responses to oxycodone and paracetamol were assumed to be independent, as inter-occasion variability of the measured pharmacodynamic responses is large, no pharmacokinetic data were obtained and the two drugs have different mechanisms of action.

**Bootstrap Analysis and Area-Under-The-Curve (AUC) Calculation**

A bootstrap validation procedure was performed to obtain the probability distributions of model parameters and derived parameters, such as $T_{\text{MAX}}$ and AUC. One-thousand bootstrap data sets were simulated by including 12 random subjects to the oxycodon group and 12 random subjects to the paracetamol group. Model parameters and derived...
parameters were estimated from each bootstrap data set. Quantiles of the parameter distributions were calculated using the statistical program R, and yielded 95% confidence intervals, and medians for internal validation.

As a measure of effect, AUCs were calculated as follows:

for $k_{ON} = k_{OFF}$: $AUC = \frac{EFF \cdot e^{[k_{ON} \cdot (1-\cosh - k_{OFF} \cdot T_{END}) \cdot e^{(-k_{ON} \cdot T_{END})}]}}{1}$,  \hspace{1cm} (A5)

for $k_{ON} \neq k_{OFF}$: $AUC = \frac{(1-e^{-k_{OFF} \cdot T_{END}}) / k_{OFF} - (1-e^{-k_{ON} \cdot T_{END}}) / k_{ON}}{[(k_{ON} / k_{OFF})^{(1-e^{-k_{OFF} \cdot T_{END}}) / k_{OFF}} - (k_{ON} / k_{OFF})^{(1-e^{-k_{ON} \cdot T_{END}}) / k_{ON}}]}$  \hspace{1cm} (A6)

where $T_{END}$ is the end of study time (300 min). All AUC's given are divided by the 300 (the duration in min of the study) to give an average end-point value over time.

**Side effects**

Heart rate and oxygen saturation (using a finger pulse oximeter) were monitored throughout the studies. In case of oxygen saturation levels below 94%, oxygen could be administered through a facemask. All incidences of nausea, vomiting and dizziness/lightheadedness were scored; all none expected side effects were noted as well.

![Figure 1](image)

**Figure 1** Mean treatment responses (± standard error of the mean) for pain tolerance (A), pain threshold (B) and pain pressure pain (C). *p = 0.02. At $t = 0$, the treatment was administered.
RESULTS

Twelve volunteers were enrolled and completed the study with mean age 22 (range 18-31) years, weight 68 (53-94) kg and height 174 (160-199) cm. In none of the subjects respiratory issues were clinically observed.

Conventional analysis

In Figure 1 the mean responses are given for all three pain indices. Significant treatment and treatment x time effects were observed for EPTol (p < 0.001), EPTh (p < 0.01) and PPTh (p < 0.01). For EPTol a significant difference between OOT and POT responses was observed from t = 45 to t = 170 min (from t = 45 to 55 min, p < 0.05; from t = 65 to 170 min, p < 0.01). In contrast, for EPTh a difference in effect between treatments was observed at t = 65 only (p=0.02). For PPTh treatments differed at t = 30 (p < 0.001), 60 (p = 0.01) and 90 min (p = 0.02). The AUC differed only for EPTol between treatments: OOT 9.2 ± 2.2 vs. POT 2.1 ± 1.0 (p < 0.05). Variability in the responses was large with the greatest variability observed for EPTh (coefficient of variation of the AUC of the measured pain response data = 61-87%), followed by EPTol (60-64%) and PPT (32-51%) (Figure S1).

Pharmacodynamic analysis

As judged by the eye, the data were adequately fitted by the pharmacodynamic model, irrespective of end-point or treatment. For both treatments, best, median and worst data fits for electrical pain tolerances are given in Figures 2 (OOT) and S2 (POT) with the corresponding data fits for electrical pain threshold and pressure pain threshold. The model parameter estimates are given in Table 1.

Transcutaneous electrical stimulation

20 mg OOT produced an increase in EPTol and EPth response currents but its effect on pain tolerance was more potent (parameter EFF is 2.2 greater for tolerance than threshold, Table 1). For both indices, the 500 mg paracetamol orodispersible tablet produced about 14% of the analgesic efficacy of oxycodone. The response profile over time was similar for paracetamol and oxycodone and for threshold and tolerance with identical values for k_on and k_off (paracetamol vs. oxycodone and tolerance vs. threshold, \( \chi^2 \)-test: \( p > 0.05 \)). The onset and offset of the response differed significantly (p<0.01) with a more rapid onset (t, k_on = 45 min) than offset (t, k_off = 154 min).
Figure 2  Examples of oxycodone data fits. Best (A), median (C) and worst (E) data fits of electrical pain tolerance data (as determined by the coefficient of determination, R²) are shown, with corresponding fits for electrical pain threshold (A, C and E) and pain pressure threshold (B, D, F). Closed circles denote the measured electrical pain tolerance data, open circles the measured electrical pain threshold data, open squares the measured pressure pain threshold data. The lines are the data fits.
Pressure Pain Assay
The effect of OOT on pressure pain threshold was comparable to that on the electrical pain threshold in terms of potency (parameter EFF for both indices \( \approx 0.4 \), Table 1). Paracetamol’s analgesic effect relative to that of oxycodone was not different from that observed in the electrical pain assay. In contrast to the observations in the electrical pain model, the rate constants for onset and offset did not differ (\( t_{1/2}k = t_{1/2}k_{ON} = t_{1/2}k_{OFF} = 30 \) min, \( p > 0.05 \)). The k-value was similar in paracetamol and oxycodone treatment groups.

Population responses
Population pharmacodynamic responses are given in Figures 3A and B, showing the difference in effect of treatment on the magnitude and the temporal profile between (and within) electrical and pressure pain models. In panels C and D of Figure 3, the percentage change relative to baseline of the oxycodone responses are plotted. The time to an increase in baseline responses of 30% are given as an index of clinical relevant effect.\(^{10,11}\) For electrical pain, a 30% increase was observed at \( t = 15 \) and 41 min for EPTol and EPTh respectively; for pressure pain at \( t = 18 \) min.

Bootstrap analysis
The results of the bootstrap validation process are given in Table S1, showing good correspondence with the pharmacodynamic parameter estimates (Table 1). Additional values were computed including \( T_{\text{MAX}} \) (time of peak analgesic effect; 111 and 43 min in the electrical and pressure pain models, respectively, for both treatments) and the various AUCs.

Side effects
Following oxycodone administration, five subjects experienced nausea, two of which vomited. Three subjects experienced dizziness/lightheadedness. In none of the subjects saturation levels dropped below 94%. Following paracetamol administration, one subject became nauseated.
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Table 1 Parameter estimates of the longitudinal pharmacodynamic model

<table>
<thead>
<tr>
<th></th>
<th>Estimate ± SE</th>
<th>$\omega^2$ ± SE</th>
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<tr>
<td><strong>Electrical pain threshold and tolerance</strong></td>
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<tr>
<td>Baseline threshold (mA)</td>
<td>8.9 ± 1.3</td>
<td>0.46 ± 0.10</td>
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<tr>
<td>Baseline tolerance (mA)</td>
<td>12.6 ± 1.5</td>
<td>0.40 ± 0.09</td>
</tr>
<tr>
<td>$k_{ON}$ (Electrical Pain) (min$^{-1}$)</td>
<td>0.015 ± 0.003</td>
<td>0.48 ± 0.30</td>
</tr>
<tr>
<td>$k_{ON}$ (Electrical Pain)/$k_{OFF}$ (Electrical Pain)</td>
<td>2.44 ± 1.90</td>
<td>3.60 ± 2.63</td>
</tr>
<tr>
<td>EFF threshold*</td>
<td>0.43 ± 0.15</td>
<td>1.20 ± 0.54</td>
</tr>
<tr>
<td>EFF tolerance*</td>
<td>0.96 ± 0.32</td>
<td>0.42 ± 0.21</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>1.88 ± 0.31</td>
<td>-</td>
</tr>
<tr>
<td><strong>Pressure pain threshold</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline value (gf)</td>
<td>422 ± 29</td>
<td>0.19 ± 0.05</td>
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<tr>
<td>$k_{(Pressure Pain)}/k_{ON}(Electrical Pain)$ #</td>
<td>1.50 ± 0.20</td>
<td>-</td>
</tr>
<tr>
<td>EFF*</td>
<td>0.40 ± 0.09</td>
<td>0.49 ± 0.24</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>57.5 ± 8.4</td>
<td>-</td>
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<tr>
<td><strong>Trend term</strong></td>
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<tr>
<td>TRD (mA/min)</td>
<td>0 (FIX)</td>
<td>0.04 ± 0.04</td>
</tr>
</tbody>
</table>

**Paracetamol versus Oxycodone**

* Relative paracetamol effect (%) | 14.1 ± 4.8 | - |

Values are median ± SE. $k_{ON}$ is the rate constant of the waxing response, $k_{OFF}$ is the rate constant of the waning response. # for pressure pain $k = k_{ON}(Pressure Pain) = k_{OFF}(Pressure Pain)$. * EFF is the oxycodone effect with the relative paracetamol effect as % of the oxycodone EFF. $\omega^2$ is the between-subject variability (in the log-domain), $\sigma$ is the variance of the residual error. TRD is a trend term.
DISCUSSION

The analgesic effect of orodispersible oxycodone was quantified with a mathematical model of analgesia evolution based on a modified Bateman function. The oxycodone formulation displayed analgesia greater than placebo with a faster onset than offset for electrical pain ($t_{1/2, k_{ON}} = 45\) min, $t_{1/2, k_{OFF}} = 154\) min) but similar onset and offset values for pressure pain (both 30 min). The analgesia efficacy parameter showed that oxycodone produced greater analgesia as determined from EPTol (EFF = 2.2) than either EPTh or PPTH (EFF = 0.4). Paracetamol had little effect on any of the three end-points (analgesic effect 14% of that of oxycodone).

Conventional statistical analysis versus longitudinal analysis

Most clinical studies on the efficacy of acute pain medication test pain relief at fixed time points following the intake of study medication by comparing the effect to placebo using t- or comparable tests at predefined time points. For example, Schachtel et al.5 used an onset-of-action model to assess the onset of analgesia by the flurbiprofen lozenge in patients with a sore throat by performing pain intensity assessments at 2-min intervals (30 measurements per hour). They observed first significant pain relief by conventional analysis (i.e. pain relief from treatment > placebo) at $t = 26\) min, while patients perceived reduction of throat pain already after 12 min. Our analysis allows assessment of the temporal profile using a sparse data sampling approach (for example, just 7 measurements in 5 hours were obtained using the pain pressure method). Despite the relatively restricted number of assessments, a reliable estimation of onset and offset (in terms of rate constants) of oxycodone effect could be made. Furthermore, the analysis allows estimation of times to a specific predefined response effects, such as a 30 or 50% increase in response thresholds. We present the 30% change in response thresholds (Figure 3) that, although somewhat arbitrary, is considered by us equivalent to a clinical significant effect in clinical trials, defined by a 30% reduction in pain indices.10 The 30% increase in response thresholds was observed after 15 (EPTol), 41 (EPTh) and 18 min (PPTH) (Figure 3). Using conventional statistics, significant differences relative to placebo were first observed after 45 (EPTol), 65 (EPTh) and 30 min (PPTH). Finally, our pharmacodynamic analysis, in contrast to conventional statistical analysis, gives a parameter for magnitude of effect (EFF), which allows comparison to other compounds (such as the comparison to the active placebo comparator in our current study or comparison among other strong opioids).
Experimental versus patient studies

In contrast to others (e.g. Rauck et al.\textsuperscript{5}; Schachtel et al.\textsuperscript{3}), we did not assess pain relief in pain patients but performed our studies in healthy volunteers. Our approach is not only more practical but it yields data not contaminated by various patient-related factors. One such factor is the presence of large variability in pain over time within and among pain patients.\textsuperscript{8} Other factors include co-medication, underlying disease (for example, repetitive hypoxic events due to sleep-related breathing disorders may enhance opioid sensitivity)\textsuperscript{5} and past experiences with pain medication. Since the pain stimuli we applied are different from pathophysiological pain, the question remains whether our analysis also applies to patients. We argue that the temporal profile we observed may be applicable to patients as well, albeit with some caution. We previously assessed the

Figure 3 The simulated typical pharmacodynamic response to 20 mg oxycodone (blue lines) and 500 mg paracetamol (orange lines) orodisperisble tablets. (A) Electrical pain tolerance (continuous lines) and electrical pain threshold (broken lines). (B) Pain pressure threshold. (C) Electrical pain tolerance (continuous lines) and electrical pain threshold (broken lines) as percentage of the baseline value. The times to an increase of 15% in tolerance and threshold responses are 6.5 and 14.5 min, respectively. (D) Pain pressure threshold as percentage of baseline value. The time to 15% increase in response pressure is 7 min. At \( t = 0 \) the treatment was administered.
temporal profile of the morphine analgesia in healthy volunteers using an electrical pain assay and observed an effect half-life for pain threshold of 1.6 h.14 Mazoit et al. observed a similar value (1.7 h) in patients being treated with morphine for postoperative pain.16 These data suggest similarities in the temporal profile of drug-induced pain relief using experimental and clinical pain as study end-points. Still, caution in blind extrapolation of our results is warranted and we will perform a patient study to validate our current results.

The modified pharmacodynamic model
We previously performed a longitudinal analysis of the effect of capsaicin 8% topical treatment in patients with postherpetic neuralgia.8 The current analysis is a modification to the previous one. This was deemed necessary since in the previous analysis both the AUC of the response and the maximal effect of the Bateman function (BF) depend on $k_{on}$ and $k_{off}$. Consequently, this implies that parameter EFF, a measure of potency, is confounded by the onset and offset characteristics causing difficulty in its interpretation.

The modified Bateman function is normalized in such a way that its minimum value is 0 and its maximum value is 1, independent of $k_{on}$ and $k_{off}$, so that parameter EFF indicates the maximum effect possible (at the dose administered).

Comparing oxycodone to paracetamol
Pain trials are commonly performed with either a placebo or active comparator. In the current study we applied an active comparator, the paracetamol orodispersible tablet. As expected, paracetamol at this low dose produced a relatively small analgesic effect in any of the end-points with 14% efficacy compared to oxycodone. Just 8/12 subjects in the electrical pain model and 3/12 in the pressure pain model showed modest analgesic responses following POT. Similar observations were reported previously by Moore et al. on paracetamol.17 Hence, taken the lack of a significant “placebo” effect, the use of the weak POT served as an effective method to blind the study. In future studies comparators such as intranasal fentanyl or orodispersible buprenorphine may be used which allows the same blinding but with a greater analgesic effect.

Interestingly, we observed that two subjects did not respond to oxycodone treatment in both nociceptive models. We relate this to genetic factors, probably reduced activity of the CYP2D6 enzyme, which causes less production of oxycodone’s active metabolite oxymorphone (the data from both subjects were included in the analyses). Zwisler et al. showed in healthy volunteers that reduced CYP2D6 activity is associated with reduced antinociceptive responses.18
Figure 4  (A) EFF parameter values (see eq. (A1)) from the electrical pain tolerance data analysis (x-axis) plotted against EFF values from the electrical pain threshold data analysis (y-axis). Pearson’s correlation coefficient ($\rho$) = 0.86, $p < 0.0001$. (B) EFF parameter values from the electrical pain tolerance data analysis (x-axis) plotted against EFF values from the pressure pain threshold data analysis (y-axis). $\rho$ = 0.13, $p = 0.53$. (C) The coefficient of determination from electrical pain tolerance data fits (x-axis) plotted against the coefficient of determination derived from electrical pain threshold data fits. $\rho$ = 0.68, $p < 0.01$. (D) The coefficient of determination from electrical pain tolerance data fits (x-axis) plotted against the coefficient of determination from pressure pain threshold data fits. $\rho$ = 0.22, $p = 0.31$. (A-D) Each dot represents data from one individual. (A and C) The continuous line is the linear regression curve ± 95% confidence interval.

Electrical pain versus pressure pain models
The effect of OOT on the electrical and pressure pain models differed in temporal profile with a more rapid analgesic onset/offset observed in the pressure pain model (Tables 1 and S1, Figures 3A and B). To further explore possible differences among these nociceptive models we compared the individual potency (EFF) and residual variability ($R^2$) estimates
of the three indices that were measured (Figure 4). As expected we observed a close correlation between EPTol and EPth values for potency (Figure 4A) and variability (Figure 4C). No correlation was present between PPT and EPTol potency and variability estimates (Figures 4B, 4D), a clear indication of the neurophysiological differences between the electrical and pressure pain assays. While skin pressure pain elicits activation of Aδ and C-fibers, electrical pain stimulation of the skin bypasses the nerve endings and direct stimulation of the sensory and non-sensory nerves occurs, with also differentiation in central processing and modulation. It is therefore within expectation that oxycodone interacts differently between the two pain models. While pressure pain has the advantage of being more physiological, the electrical stimuli are easily controlled and consequently the electrical nociceptive model is widely used, especially in pharmacological trials.

CONCLUSIONS

Orodispersible oxycodone 20 mg produced analgesic effects in two experimental pain models that was well described by a novel mathematical pharmacodynamic model in terms of onset and offset of effect and analgesic efficacy, despite sparse data sampling. This analytical approach has advantages over conventional statistical analyses as it, for example, allows the accurate estimation of the response times to specific events such as the time to a 30% (a measure of clinical importance) increase in response thresholds. For OOT, the response to a 30% increase in response threshold was rather variable and ranged from 15 to 41 min, depending on the end-point chosen. Future studies should incorporate patients and potent opioid comparators.
REFERENCES


Supporting Information

Additional Supporting Information was published in the online version of this article:

Figure S1 Influence of 20 mg oxycodone and 500 mg paracetamol orodispersible tablets on electrical pain threshold (A and D), electrical pain tolerance (B and E) and pressure pain threshold (C and F). Grey and red lines are the individual and median responses, respectively. At t = 0, the treatment was administered.
Figure S2 Examples of paracetamol data fits. Best (A), median (C) and worst (E) data fits of electrical pain tolerance data (as determined by the coefficient of determination, R²) are shown, with corresponding fits for electrical pain threshold (A, C and E) and pain pressure threshold (B, D, F). Closed circles denote the measured electrical pain tolerance data, open circles the measured electrical pain threshold data, open squares the measured pressure pain threshold data. The lines are the data fits.
### Supplemental Table 1  Results of the bootstrap analysis

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<td>Baseline threshold (mA)</td>
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<tr>
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</tr>
<tr>
<td>$T_{MAX}$ (min)</td>
<td>75</td>
<td>111</td>
<td>170</td>
</tr>
<tr>
<td>AUC/300 threshold oxycodone (mA/min)</td>
<td>0.147</td>
<td>0.337</td>
<td>0.706</td>
</tr>
<tr>
<td>AUC/300 tolerance oxycodone (mA/min)</td>
<td>0.322</td>
<td>0.732</td>
<td>1.400</td>
</tr>
<tr>
<td>AUC/300 threshold paracetamol (mA/min)</td>
<td>0.019</td>
<td>0.051</td>
<td>0.090</td>
</tr>
<tr>
<td>AUC/300 tolerance paracetamol (mA/min)</td>
<td>0.040</td>
<td>0.112</td>
<td>0.201</td>
</tr>
<tr>
<td><strong>Pressure Pain Threshold</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (gf)</td>
<td>364</td>
<td>421</td>
<td>487</td>
</tr>
<tr>
<td>$t_{1/2}k$ (min) *</td>
<td>16</td>
<td>30</td>
<td>48</td>
</tr>
<tr>
<td>EFF oxycodone</td>
<td>0.21</td>
<td>0.40</td>
<td>0.67</td>
</tr>
<tr>
<td>EFF paracetamol</td>
<td>0.03</td>
<td>0.06</td>
<td>0.10</td>
</tr>
<tr>
<td>$T_{MAX}$ (min)</td>
<td>24</td>
<td>43</td>
<td>70</td>
</tr>
<tr>
<td>AUC/300 oxycodone (gf/min)</td>
<td>0.093</td>
<td>0.218</td>
<td>0.408</td>
</tr>
<tr>
<td>AUC/300 paracetamol (gf/min)</td>
<td>0.012</td>
<td>0.031</td>
<td>0.061</td>
</tr>
<tr>
<td><strong>Overall relative paracetamol effect</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effect (%)</td>
<td>7.0</td>
<td>14.8</td>
<td>30.1</td>
</tr>
</tbody>
</table>

* for pressure pain: $k = k_{ON} = k_{OFF}$