Research Square

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Drug exposure during oxycodone patient-controlled analgesia with adjuvant dexmedetomidine after lumbar spinal fusion

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Abstract

Background

We characterized dexmedetomidine and oxycodone exposure during postoperative patient-controlled analgesia (PCA). Two additional analyses addressed the relationships between current pain and subsequent oxycodone administration and between measured oxycodone concentration and analgesia at the time of sampling.

Methods

This analysis included 98 patients from a randomized, double-blind, placebo-controlled dose-response trial after lumbar spinal fusion. PCA contained oxycodone 1 mg/mL alone or with dexmedetomidine 2.5, 5, or 10 μg/mL. Plasma dexmedetomidine, oxycodone, and major metabolite concentrations were characterized over 24 h with high-performance liquid chromatography tandem mass spectrometry. Associations of resting pain with subsequent PCA-administered oxycodone and of measured oxycodone concentration with adequate analgesia (numerical rating scale at rest ≤ 4) were analysed using linear and logistic mixed-effects models, respectively.

Results

Oxycodone concentrations showed marked between-patient variability, while noroxycodone and noroxymorphone increased progressively and oxymorphone remained lower. Dexmedetomidine concentrations separated clearly according to randomized dose. Higher current resting pain was associated with greater subsequent oxycodone administration ($P < 0.001$). A 3-point higher resting NRS was associated with approximately 1.1–1.2 mg greater oxycodone administration over the following 3–4 h and 5.2 mg over the subsequent 16 h. Higher measured oxycodone concentration was associated with lower odds of adequate analgesia (odds ratio 0.377 per concentration doubling; 95% CI 0.24–0.59; $P < 0.001$).

Conclusions

During postoperative PCA, higher current pain was associated with greater subsequent oxycodone administration. The association between measured oxycodone concentration and analgesia cannot be interpreted as a simple pharmacological concentration–effect relationship.

Trial registration

ClinicalTrials.gov, NCT02454881 (https//clinicaltrials.gov/study/NCT02454881) EudraCT 201400325231.

INTRODUCTION

Patient-controlled analgesia (PCA) is an established method of postoperative opioid administration. It allows patients to self-administer intravenous opioid doses within predefined safety limits [1]. Compared with conventional systemic opioid administration, PCA provides slightly better pain control and greater patient satisfaction, although opioid consumption may be somewhat higher [2]. Oxycodone is effective for intravenous PCA and is well characterized as a postoperative analgesic [3, 4, 5]. Non-opioid adjuvant drugs have been added to opioid PCA to improve analgesia or reduce opioid requirements. These include S-ketamine and dexmedetomidine [6, 7, 8, 9].

PCA differs from a predetermined opioid regimen because the patient contributes to the dosing history. Opioid requirements vary substantially between patients and are associated with pain and patient characteristics [10, 11]. Together with drug disposition, dosing history determines subsequent systemic exposure. Plasma oxycodone concentration is a pharmacologically relevant measure of exposure. Clinical pharmacokinetic–pharmacodynamic studies have shown associations between oxycodone exposure and analgesic effect [12, 13, 5]. The setting of postoperative PCA complicates this relationship. A measured concentration reflects preceding patient-controlled dosing, while pain and recovery change over the same period. The association between measured opioid exposure and pain intensity may therefore not reflect a simple unidirectional pharmacological concentration–effect relationship. Pain intensity and opioid consumption are also not interchangeable measures of the postoperative state. In a separate lumbar fusion cohort, we recently found that preoperative emotional stress was associated with severe postoperative pain but not with oxycodone consumption [unpublished].

Less is known about how opioid exposure relates to pain during patient-controlled dosing. Pain may influence subsequent opioid administration, while the measured concentration reflects the dosing history that preceded it. It remains unclear how current postoperative pain relates to subsequent patient-controlled oxycodone administration and how measured oxycodone exposure relates to the pain state during PCA.

The DoseRespDex trial included repeated measurements of dexmedetomidine, oxycodone and its major metabolites, pain intensity, and cumulative PCA-administered oxycodone during the first 24 h after lumbar spinal fusion surgery [9]. In the present exploratory analyses, we first characterized the plasma concentration profiles of dexmedetomidine, oxycodone, and its major metabolites. We then examined whether current resting pain was associated with subsequent patient-controlled oxycodone administration and, separately, how measured oxycodone concentration was associated with pain at the time of sampling. The analyses were not designed to establish a causal concentration–effect relationship.

METHODS

Study design and clinical data

This study was conducted as part of the DoseRespDex trial (ClinicalTrials.gov NCT02454881; EudraCT 2014-003252-31). DoseRespDex was a single-centre, randomized, double-blind, placebo-controlled dose-response trial in adults undergoing elective lumbar spinal fusion at Turku University Hospital, Finland. The study was approved by the Institutional Review Board of the Hospital District of Southwest Finland (110/1800/2014; approved on 21.5.2015) and the Finnish Medicines Agency (FIMEA, KL 28/2015), and all participants provided written informed consent. The study design, eligibility criteria, perioperative management, randomization, and clinical outcomes have been reported previously [9]. This manuscript complies with the Consolidated Standards of Reporting Trials guidelines (CONSORT).

Patients were randomized 1:1:1:1 to intravenous PCA with oxycodone 1 mg/mL alone (D0) or combined with dexmedetomidine 2.5 μg/mL (D2), 5 μg/mL (D5), or 10 μg/mL (D10) during the first 24 postoperative hours. The stability and compatibility of the oxycodone–dexmedetomidine PCA mixtures have been reported separately [14]. PCA delivered 1-mg oxycodone boluses with a 5-min lockout interval and no background infusion. After 24 h, PCA was continued with oxycodone alone as described in the parent trial. Resting pain intensity was assessed using an 11-point numerical rating scale (NRS), ranging from 0 (no pain) to 10 (worst imaginable pain).

The present analysis used the final DoseRespDex analysis population of 98 patients. Previously reported clinical efficacy and safety outcomes were not re-analysed as endpoints of the present study. Summaries of plasma dexmedetomidine concentrations have previously been reported in relation to the haemodynamic and respiratory effects of the randomized intervention [15].

Blood sampling and bioanalysis

Blood samples for drug concentration measurements were obtained at baseline and at nominal times of 5 min, 1 h, 4 h, 8 h, and 24 h after initiation of PCA. Plasma concentrations of dexmedetomidine, oxycodone, noroxycodone, oxymorphone, and noroxymorphone were determined at the Bioanalytical Laboratory, Institute of Biomedicine, University of Turku, Finland, using quantitative high performance liquid chromatography-tandem mass spectrometry (HPLC–MS/MS) methods. Full analytical methods are provided in Additional file 1.

Dexmedetomidine was extracted from 250 μL of plasma by solid-phase extraction using Sep-Pak tC18 96-well plates, with medetomidine-d3 as the internal standard. Chromatographic separation was performed on a Gemini C18 column, followed by positive-ion electrospray tandem mass spectrometric detection using a Sciex ExionLC AD system coupled to a Qtrap 6500 + triple-quadrupole mass spectrometer. The calibration range was 0.02–5.0 ng/mL and the lower limit of quantification (LLOQ) was 0.02 ng/mL. Inter-assay accuracy across quality-control samples was 97.1–105%, with coefficients of variation of 2.42–7.54%.

Oxycodone, noroxycodone, oxymorphone, and noroxymorphone were extracted from 200 μL of plasma by solid-phase extraction using Sep-Pak tC18 96-well plates and stable-isotope-labelled internal

standards. Chromatographic separation was performed on a Kinetex EVO C18 column using the same HPLC–MS/MS system. The calibration range was 0.05 to 50 ng/mL for all four analytes, with an LLOQ of 0.05 ng/mL. Across quality-control samples, inter-assay accuracy ranged from 89.8–109% for oxycodone, 87.8–105% for noroxycodone, 89.1–105% for oxymorphone, and 93.2–103% for noroxymorphone. Corresponding inter-assay coefficients of variation were 4.44–13.5%, 5.25–10.2%, 3.27–10.1%, and 4.54–11.6%, respectively.

Data analysis

Clinical and laboratory data were linked by patient and protocol-defined nominal sampling time. The final analysis population comprised 98 patients (D0, n = 25; D2, n = 24; D5, n = 24; D10, n = 25). Quantified concentrations were used as measured. Below limit of quantitation (BLQ) concentrations at baseline and dexmedetomidine BLQ concentrations in D0 were represented as zero; other post-dose BLQ concentrations were represented as one-half of the analyte-specific lower limit of quantification. Missing or analytically unusable observations remained missing, and no concentration, PCA administration, or NRS values were imputed, interpolated, or reconstructed. For analyses requiring both concentration and clinical data, observations were matched at 1, 4, 8, and 24 h.

Statistical analysis

Analyses were exploratory. Plasma concentrations of dexmedetomidine, oxycodone, noroxycodone, oxymorphone, and noroxymorphone were summarized descriptively over time using individual trajectories and median profiles by randomized treatment group.

The association between current resting pain and subsequent patient-controlled oxycodone administration was examined over the 1–4, 4–8, and 8–24 h intervals. Subsequent oxycodone administration was defined as the increment in cumulative PCA-administered oxycodone during each interval. A linear mixed-effects model was fitted with resting NRS at interval start, interval, and randomized treatment group as fixed effects and patient as a random intercept. Because oxycodone dose increments were right-skewed, the outcome was transformed (logarithmic) before modelling. A small constant (0.5 mg) was added before log transformation to retain the three intervals with zero oxycodone administration.

For clinical interpretation, model predictions were back transformed to arithmetic mean oxycodone doses in milligrams. The calculation accounted for both between-patient variability and residual variability, and predictions were averaged across the four randomized treatment groups according to their proportions in the study population. To obtain 95% confidence intervals, we performed a parametric bootstrap analysis with 2,000 replicates. Fixed effects and variance components were re-estimated in each replicate.

The association between measured plasma oxycodone concentration and adequate analgesia (resting NRS ≤ 4) was examined at 1, 4, 8, and 24 h using logistic mixed-effects regression. Log-transformed

oxycodone concentration, nominal time, randomized treatment group, and the concentration-by-time interaction were included as fixed effects, with patient as a random intercept. The interaction was assessed by likelihood-ratio testing, and in the absence of evidence for interaction, the corresponding reduced model was used to estimate the common concentration association. The concentration effect was expressed as an odds ratio per doubling of measured oxycodone concentration, with model-based marginal probabilities used for graphical interpretation.

Model assumptions were assessed using residual and simulation-based diagnostics, including evaluation of residual distributions, heteroscedasticity, and influential observations where applicable. Effect estimates are presented with 95% confidence intervals and nominal two-sided p values. Given the exploratory nature of the analyses, no adjustment for multiple testing was applied. Analyses were performed in R [version 4.5.2; R Foundation for Statistical Computing, Vienna, Austria].

Use of generative AI

During the preparation of this manuscript, the authors used ChatGPT (OpenAI) to assist with language editing and improving readability. The authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

RESULTS

This exploratory analysis included 98 patients from the original randomized trial: 25 in the oxycodone-only placebo group (D0) and 24, 24, and 25 in the groups receiving dexmedetomidine 2.5 µg/mL (D2), 5 µg/mL (D5), and 10 µg/mL (D10), respectively. The median age was 60 years (range 28–78), and 56 patients (57%) were female. Plasma concentrations of dexmedetomidine, oxycodone, noroxycodone, oxymorphone, and noroxymorphone were assessed at the protocol-defined sampling times from baseline to 24 h. Concentration data were analysed according to the predefined analyte-specific eligibility and BLQ rules, without interpolation or reconstruction of missing samples.

Current resting pain and subsequent patient-controlled oxycodone administration

Higher current resting pain was associated with greater subsequent patient-controlled oxycodone administration. There was no evidence that this association differed across the 1–4, 4–8, and 8–24 h intervals (NRS-by-interval interaction: $F = 0.596$, $p = 0.55$). In the reduced model assuming a common association across intervals, the coefficient for resting NRS was 0.061 (95% CI 0.025–0.096; $p < 0.001$) on the log-transformed oxycodone dose scale (Table 1).

Table 1
Main exploratory findings

Analysis	Data	Temporal heterogeneity		Common association		
		Test statistic	p-value	Effect estimate	95% CI	p-value
Current resting pain and subsequent PCA oxycodone administration						
	98 patients; 292 observations	NRS × interval: F = 0.596	0.55	β = 0.061	0.025–0.096	< 0.001
Measured oxycodone concentration and adequate analgesia						
	98 patients; 387 observations	Concentration × time: χ^2 = 1.60; df = 3	0.66	OR per doubling = 0.38	0.24–0.59	< 0.001

For subsequent oxycodone administration, the predictor was NRS at rest at interval start and the outcome was subsequent PCA oxycodone dose increment; β is reported on the log(dose increment + 0.5 mg) scale. For analgesia, the predictor was measured plasma oxycodone concentration, and the outcome was adequate analgesia (NRS at rest ≤ 4).

OR; odds ratio; CI, confidence interval; df, degrees of freedom.

Model-based marginal predictions were used to express this association on the original dose scale. A 3-point higher resting NRS was associated with approximately 1.1–1.2 mg greater subsequent oxycodone administration over the following 3–4 h and approximately 5.2 mg greater administration over the subsequent 16 h (Fig. 3).

Measured oxycodone concentration and pain state

The concentration–pain analysis included 387 of 392 possible oxycodone concentration–NRS observations from the 98 patients at 1, 4, 8, and 24 h. Higher measured plasma oxycodone concentrations were associated with a lower probability of adequate analgesia, defined as resting NRS ≤ 4. There was no evidence that this association differed across postoperative sampling times (concentration-by-time interaction: likelihood-ratio χ^2 = 1.60, df = 3, p = 0.66).

In the reduced model assuming a common concentration association across sampling times, the odds ratio for adequate analgesia was 0.377 (95% CI 0.24–0.59; p < 0.001) per doubling of measured oxycodone concentration. Model-based predicted probabilities showed the corresponding inverse association between measured oxycodone concentration and adequate analgesia across the observed concentration range (Fig. 4). This association was observational and describes contemporaneous measured exposure and pain state rather than a causal concentration–analgesic effect.

DISCUSSION

In this study, we characterized the development of dexmedetomidine and oxycodone exposure during the first 24 h of postoperative PCA. We also examined how current resting pain was related to subsequent patient-controlled oxycodone administration and how measured oxycodone concentration was related to contemporaneous analgesia. Oxycodone and its metabolites showed distinct concentration–time profiles, whereas dexmedetomidine concentrations separated clearly according to randomized dose. Higher current resting pain was associated with greater subsequent patient-controlled oxycodone administration. Furthermore, higher oxycodone concentrations were associated with a lower probability of adequate analgesia. This association did not differ across postoperative sampling times. These findings indicate that postoperative pain, patient-controlled oxycodone administration, and measured plasma oxycodone concentrations represent different and interrelated aspects of analgesic treatment during PCA.

Plasma oxycodone concentrations increased rapidly after initiation of PCA and showed substantial between-patient variability, particularly during the early postoperative period. Similar variability was observed by Silvasti et al. [3] during postoperative oxycodone PCA, with plasma concentrations ranging from 0 to 100 ng/mL in the recovery room and from < 3 to 98 ng/mL at 24 h. Their study included patients undergoing lumbar spinal fusion and used PCA without a background infusion and with a 5-min lockout interval, although the oxycodone bolus was weight-based. Noroxycodone and noroxymorphone concentrations increased progressively during the 24-h observation period, whereas oxymorphone concentrations remained substantially lower and showed less increase after the first postoperative hour. This pattern is consistent with previous findings of substantial circulating concentrations of noroxycodone and noroxymorphone but considerably lower concentrations of oxymorphone after oxycodone administration [16]. Their pharmacokinetic–pharmacodynamic analysis further suggested that the observed pharmacodynamic effects were primarily attributable to oxycodone rather than its circulating metabolites [16]. In the present study, the metabolite profiles were descriptive and were not related to analgesic outcomes.

Dexmedetomidine concentrations increased after PCA initiation, with clear separation between the three active dose groups. In our previous study, a single intranasal dose of 100 µg produced a model-predicted peak concentration of 0.273 ng/mL at 98 min [17]. Dexmedetomidine administered with patient-controlled oxycodone therefore produced systemic concentrations within the same general range as a single 100-µg intranasal dose, although the two administration methods produced distinctly different concentration–time profiles. Dexmedetomidine has been evaluated as an adjunct to opioid-based intravenous PCA in several clinical trials [18], but we are not aware of previous studies reporting the plasma dexmedetomidine concentrations achieved with this mode of administration.

Our results show that higher current resting pain was associated with greater subsequent oxycodone administration. On the original dose scale, a 3-point higher resting NRS was associated with approximately 1.1–1.2 mg greater oxycodone administration over the following 3–4 h and 5.2 mg

greater administration over the subsequent 16 h. This is consistent with earlier observations during postoperative PCA. Higher pain has previously been associated with greater morphine use during postoperative PCA, although the strength of the observed relationships varied considerably between patients [19]. Opioid dosing is not externally fixed but partly reflects the patient's analgesic requirement and use of the PCA device. This distinction is important when relating measured opioid concentrations to pain ratings.

Our results show that higher measured oxycodone concentrations were associated with a lower probability of adequate analgesia. In an earlier study, no correlation between plasma oxycodone concentration and pain scores at the time of sampling was observed during postoperative oxycodone PCA [3]. Studies with other opioids have likewise shown marked between-patient variation in concentration–effect relationships during PCA, including patient-specific minimum effective concentrations [19, 20]. In contrast, clinical PK/PD studies of oxycodone have demonstrated associations between higher plasma concentrations and better postoperative analgesia [12, 13]. The inverse association observed in the present study should therefore not be interpreted as evidence of an inverse pharmacological concentration–effect relationship. Current pain was associated with subsequent oxycodone administration, while measured oxycodone concentration reflects preceding patient-controlled dosing as well as oxycodone pharmacokinetics. In this setting, the association between measured oxycodone concentration and pain does not directly represent the pharmacological effect of oxycodone.

A single plasma oxycodone concentration needs to be considered in relation to the clinical pain state and preceding dosing history, because the measured concentration reflects both drug disposition and preceding patient-controlled administration. Similarly, cumulative opioid consumption is not a direct measure of analgesic efficacy, as it reflects analgesic requirement, patient-controlled dosing behaviour, and pharmacokinetic variability. Our recent study showed that higher current pain was associated with greater subsequent PCA activity, while the relationship between oxycodone concentration and adequate analgesia varied over postoperative time [unpublished]. The present data do not define a therapeutic plasma oxycodone concentration or a minimum effective concentration. Estimation of such thresholds requires a study design that explicitly relates measured concentrations to a defined analgesic response [20, 12, 13].

Strengths of this study include the randomized parent trial with a standardized PCA regimen, drug concentration analysis, records of actual PCA administration, and repeated assessment of pain. Several limitations should also be considered. The present analyses were exploratory and were not designed to establish causal relationships. Plasma concentrations may not reflect effect-site concentrations, and the concentration–pain analysis cannot establish the temporal direction of the observed association. The limited sampling frequency further restricts characterization of short-term changes in exposure and response. Furthermore, pain intensity, opioid requirements, PCA dosing, and drug exposure change concurrently during postoperative recovery, complicating the interpretation of their associations. Finally,

we did not comprehensively examine age, weight, or other patient characteristics as determinants of oxycodone exposure, PCA use, or analgesic response.

The dexmedetomidine concentrations measured during PCA provide reference data for future studies evaluating the efficacy and safety of dexmedetomidine as an opioid adjuvant at clinically achieved exposures. However, the present study does not establish a therapeutic concentration range for dexmedetomidine or oxycodone. The findings do not support routine plasma concentration monitoring of either drug to guide postoperative PCA, for which clinical assessment remains essential.

Conclusions

Dexmedetomidine and oxycodone exposures developed with distinct concentration–time profiles during postoperative PCA. Higher current pain was associated with greater subsequent oxycodone administration. During PCA, measured plasma oxycodone concentrations reflect both drug disposition and preceding patient-controlled dosing and cannot be interpreted independently of the clinical pain state.

Abbreviations

BLQ
below the limit of quantification
CI
confidence interval
df
degrees of freedom
HPLC–MS/MS
high-performance liquid chromatography–tandem mass spectrometry
LLOQ
lower limit of quantification
NRS
numerical rating scale
OR
odds ratio
PCA
patient-controlled analgesia.

Declarations

Ethics approval and consent to participate

The study protocol was reviewed and approved by the Ethics Committee of the Hospital District of Southwest Finland 110/1800/2014 and the Finnish National Agency for Medicines (KL 28/2015). All

participants provided written informed consent before study participation.

Consent for publication

Not applicable.

Availability of data and materials

The patient-level data underlying this study are not publicly available owing to regulatory and confidentiality restrictions applicable to the original clinical trial.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Sanna Mäkelä: Investigation, Formal analysis, Data curation, Writing – original draft, Writing – review & editing.

Panu Uusalo: Investigation, Formal analysis, Data curation, Writing – review & editing.

Karla Saukkonen: Methodology, Writing – review & editing.

Antti Liukas: Investigation, Writing – review & editing.

Eliisa Löyttyniemi: Methodology, Formal analysis, Writing – review & editing.

Marica Engström: Methodology, Investigation, Validation, Writing – review & editing.

Aleksi Tornio: Methodology, Investigation, Validation, Writing – review & editing.

Teijo I. Saari: Conceptualization, Methodology, Investigation, Formal analysis, Supervision, Funding acquisition, Writing – original draft, Writing – review & editing.

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Figures

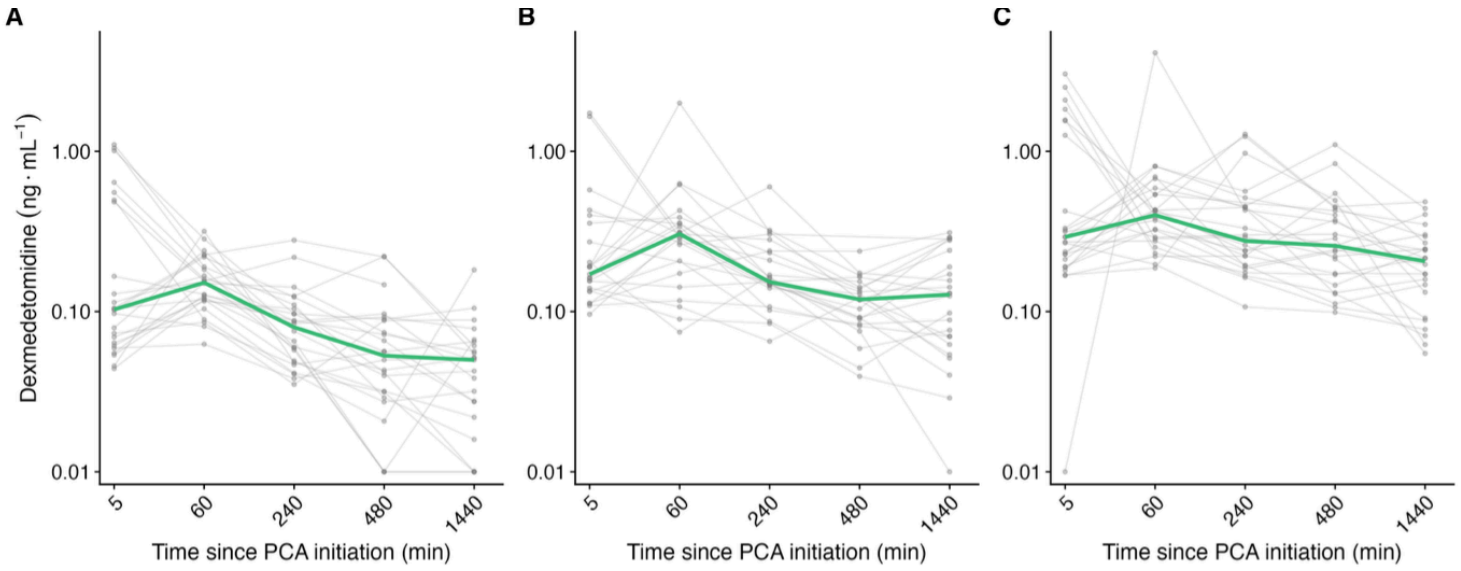


Figure 1

Plasma dexmedetomidine concentrations during patient-controlled analgesia. Individual plasma dexmedetomidine concentration–time profiles in patients randomized to dexmedetomidine (A) 2.5 µg/mL, (B) 5 µg/mL, or (C) 10 µg/mL in the oxycodone PCA solution. Grey lines and points represent individual patients and green lines the median concentration at each nominal sampling time. Concentrations are shown on a logarithmic scale. Dexmedetomidine was not detected in the oxycodone-only group (D0).

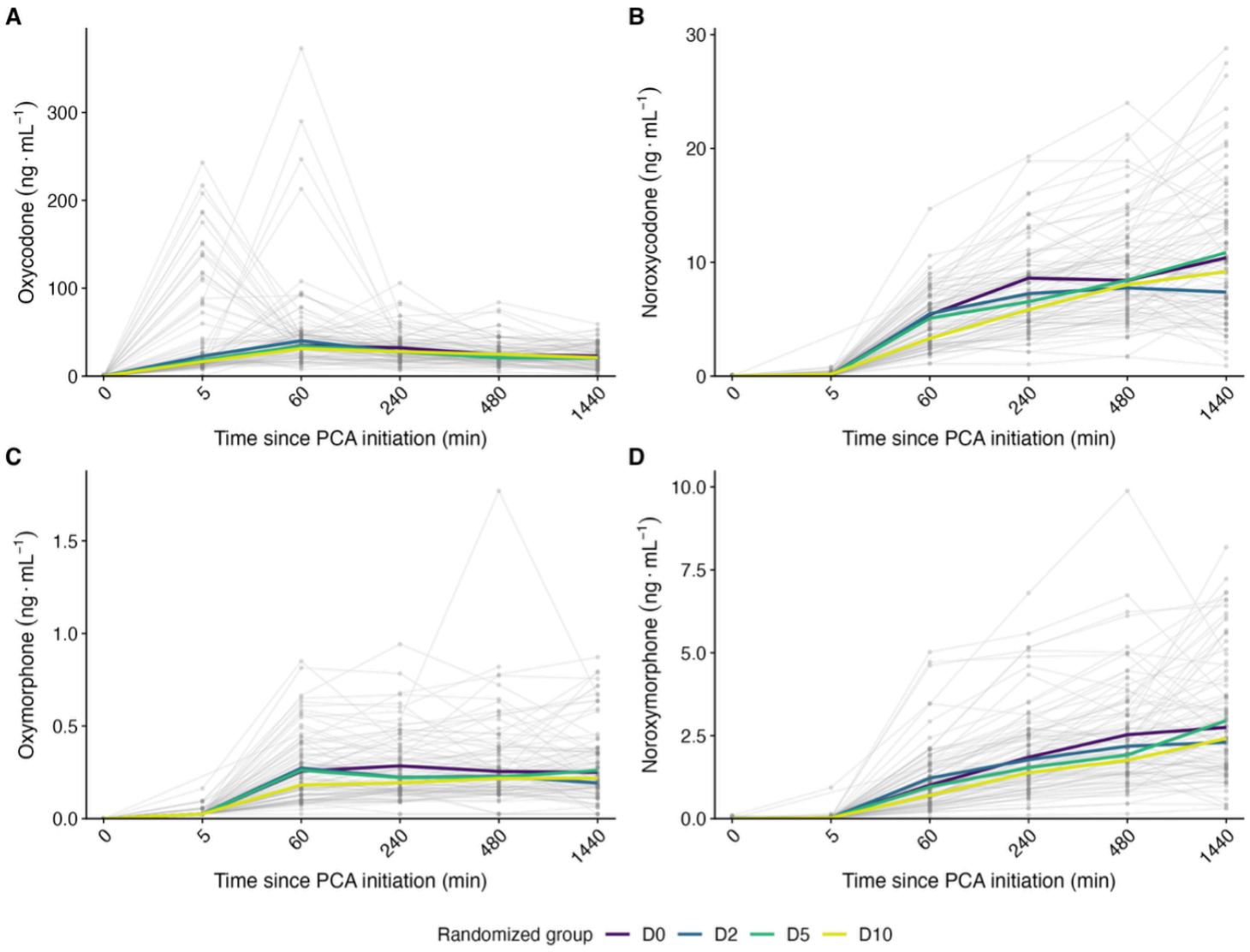


Figure 2

Plasma oxycodone and metabolite concentrations during patient-controlled analgesia. Individual concentration–time profiles of oxycodone (A), noroxycodone (B), oxymorphone (C), and noroxymorphone (D) during the first 24 h of PCA. Grey lines and points represent individual patients. Coloured lines represent median concentrations at each nominal sampling time by randomized treatment group: oxycodone alone (D0) or oxycodone with dexmedetomidine 2.5 µg/mL (D2), 5 µg/mL (D5), or 10 µg/mL (D10).

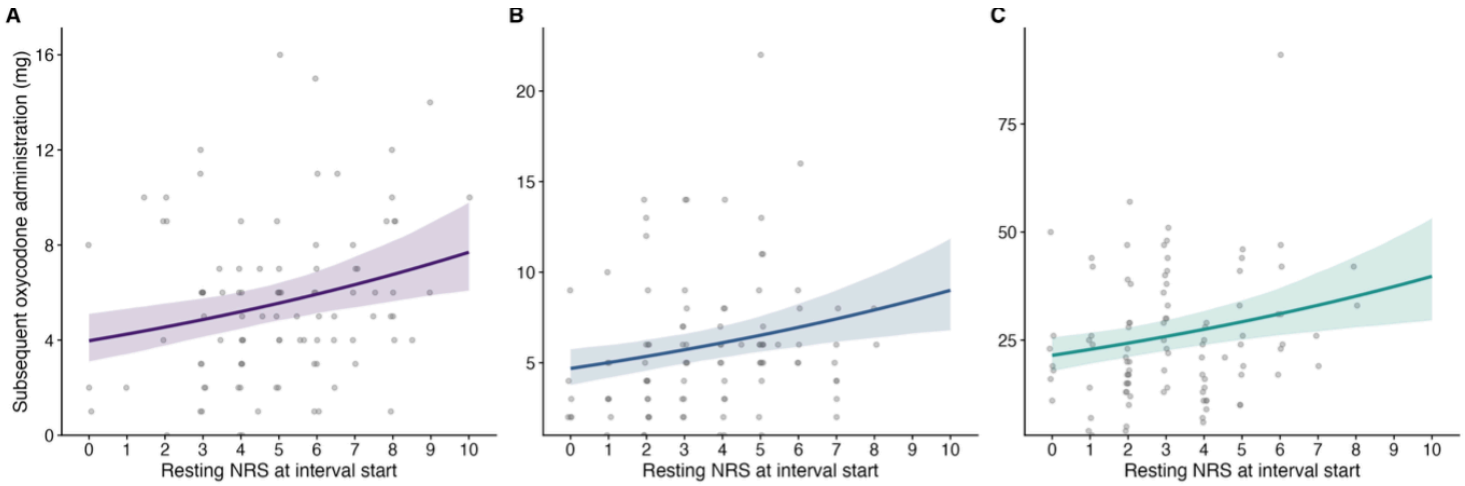


Figure 3

Association between current resting pain and subsequent patient-controlled oxycodone administration. Resting numerical rating scale (NRS) at the start of each interval and oxycodone administered during the subsequent 1–4 h (A), 4–8 h (B), and 8–24 h (C) intervals. Points represent observed patient-level data. Lines show population-marginal arithmetic mean predictions from the reduced linear mixed-effects model, expressed in milligrams and averaged across the observed randomized treatment-group distribution. Shaded areas indicate 95% confidence intervals obtained from 2,000 parametric bootstrap replicates.

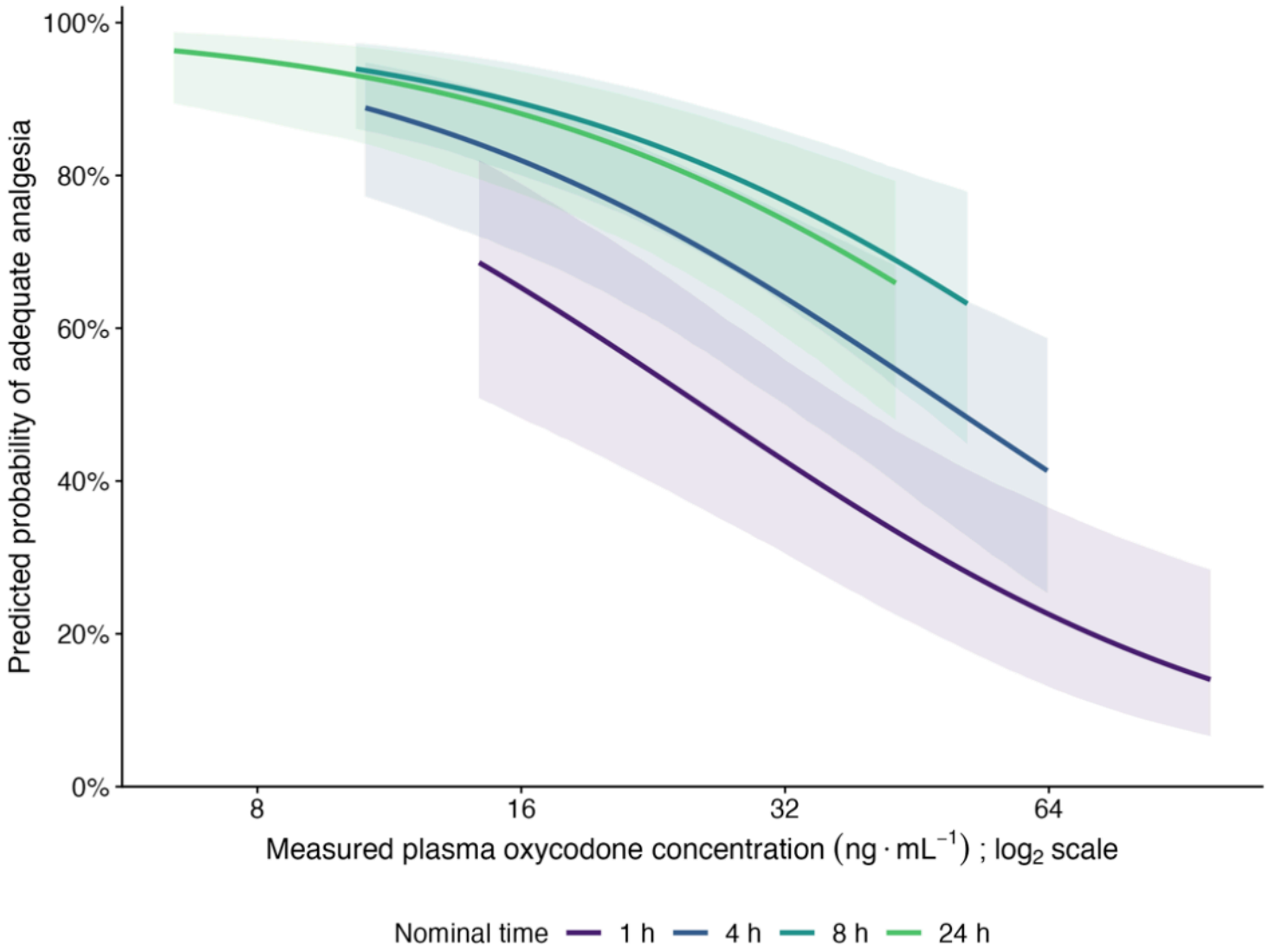


Figure 4

Association between measured plasma oxycodone concentration and adequate analgesia. Model-based predicted probability of adequate analgesia, defined as resting NRS ≤4, according to measured plasma oxycodone concentration at 1, 4, 8, and 24 h after initiation of PCA. Lines show marginal predictions from the reduced logistic mixed-effects model assuming a common concentration association across sampling times; shaded areas indicate 95% confidence intervals. Predictions are standardized over the observed randomized treatment-group distribution. Plasma oxycodone concentration is shown on a log-scale.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile1SupplementaryMethods.pdf