

# Analgesic Plasma Concentrations of Oxycodone After Surgery for Breast Cancer—Which Factors Matter?

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We investigated factors affecting analgesic oxycodone concentrations after breast cancer surgery in 1,000 women. Preoperatively, we studied heat and cold pain sensitivities and anxiety scores. Postoperatively, rest and motion pain intensities were measured and intravenous oxycodone was administered until satisfactory analgesia. At this point, the mean oxycodone concentration (variation coefficient) was 33.3 ng/mL (66%) and it was 21.7 ng/mL (69%) when the patient requested oxycodone again. At both time points, the concentrations varied >100-fold between individuals. The analgesic oxycodone concentration was increased by 21.3% per motion pain intensity score on a 0–10 scale and by 22.3% if axillary clearance was performed instead of sentinel node biopsy ( $P < 0.001$ ). Forty-seven women who were older and less anxious than others ( $P < 0.01$ ) required no oxycodone. Anxiety, age, chronic pain, or preoperative pain sensitivity were not independently associated with the analgesic oxycodone concentration. *CYP2D6* and *CYP3A* genotypes did not affect analgesic concentration or duration of analgesia.

## Study Highlights

### WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Parenteral oxycodone is increasingly used for postoperative analgesia. Individual analgesic doses of oxycodone vary significantly.

### WHAT QUESTION DID THIS STUDY ADDRESS?

☑ We examined individual analgesic plasma oxycodone concentrations and the factors affecting them in 1,000 women after they underwent breast cancer surgery.

### WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

☑ The analgesic oxycodone concentrations varied more than 100-fold. Postoperative pain intensity and type of axillary surgery markedly affected the oxycodone concentration required for satisfactory analgesia. Patients with the highest motion pain

intensity (scores 7–10/10) need nearly three times higher plasma concentrations of oxycodone than patients with low (0–3) scores. Preoperatively assessed anxiety, heat or cold pain scores, or *CYP3A*, *CYP2D6*, or *OPRM1* genotypes were not independently associated with the analgesic plasma oxycodone concentrations.

### HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE

☑ Postoperative motion pain intensity strongly predicts the oxycodone plasma concentration the patient will need for satisfactory analgesia. This information can be valuable for individualized postoperative pain relief and for the future design of pharmacogenetic studies on opioid analgesia.

Parenteral oxycodone is increasingly used worldwide. However, pharmacokinetic data of intravenous oxycodone in the management of postoperative pain are limited.<sup>1</sup> The dose of oxycodone needed for satisfactory analgesia varies remarkably between individuals.<sup>2</sup>

Several factors can affect the need for oxycodone. Different types of surgery predispose patients to variable postoperative pain intensities depending on the tissue being operated and invasiveness of surgery.<sup>3,4</sup> Moreover, high levels of anxiety are associated with increased pain sensitivity and opioid requirement.<sup>4–6</sup>

Older age increases plasma oxycodone concentrations and lowers its dose requirement.<sup>7,8</sup> This may be due to lower percentage of body water and to decreased liver and kidney function.<sup>8,9</sup> In addition, chronic nicotine exposure may increase postoperative pain intensity and opioid consumption, possibly due to adaptive changes in the endogenous opioid system.<sup>10–12</sup> Abstinent tobacco-smokers also require higher opioid doses postoperatively.<sup>13</sup>

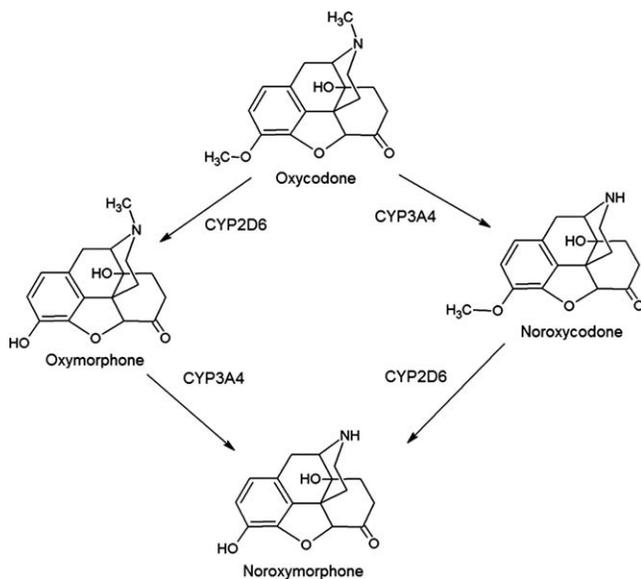
Oxycodone is metabolized by the cytochrome P450 (CYP) enzymes *CYP3A4/5* and *2D6* (Figure 1). The major pathway is

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**Figure 1** Main metabolic pathways of oxycodone.

N-demethylation by CYP3A4 to noroxycodone, which lacks opioid activity.<sup>14</sup> Metabolism via CYP2D6 yields oxymorphone, which has a strong opioid potency,<sup>14</sup> but its concentration remains very low.<sup>15</sup> Further oxidation of both noroxycodone and oxymorphone results in noroxymorphone, which is a strong  $\mu$ -opioid receptor agonist, but does not penetrate the blood-brain barrier and consequently has only peripheral effects.<sup>16</sup> Ketone reduction yields two stereoisomers of oxycodol from oxycodone, noroxycodol from noroxycodone, and oxymorphol from oxymorphone.<sup>15</sup> Oxycodone and its metabolites are excreted via the kidneys, in unconjugated and conjugated forms.<sup>15,17</sup> Inhibition and induction of CYP3A4 have had marked effects on plasma concentration of oxycodone,<sup>18,19</sup> but inhibition of CYP2D6 or genetically poor CYP2D6 metabolism have only marginally increased oxycodone concentrations.<sup>20,21</sup> In experimental pain models in healthy volunteers, CYP2D6 poor metabolizers (PMs) experienced less pain relief with oxycodone than extensive metabolizers (EMs).<sup>22</sup> However, the same research group did not find any difference in the postoperative analgesic effect of oxycodone between these two CYP2D6 phenotypes.<sup>21</sup>

Variability in genes related to pharmacodynamics may also affect the efficacy of oxycodone.<sup>23,24</sup> For example, the *OPRM1* c.118A>G (rs1799971, p.Asn40Asp) single nucleotide variation (SNV) has been found to affect postoperative oxycodone consumption, but no studies have explored its effect on the required analgesic concentrations of oxycodone.

The analgesic oxycodone concentrations have been studied only in small samples ( $\leq 50$  individuals) after abdominal surgery.<sup>25–27</sup> Our aim was to characterize analgesic plasma concentrations of oxycodone in 1,000 women after breast cancer surgery, to find out how much they vary between individuals, and what factors explain this variation. This information could be valuable for the individualized management of postoperative pain and for future pharmacogenetic studies of analgesics.

We examined 1,000 Finnish women undergoing surgery for breast cancer. In the postoperative phase, plasma oxycodone and

its main metabolite concentrations were measured when the patients considered their analgesia satisfactory for the first time by intravenous dose titration and when they requested a new dose of oxycodone. Various patient-related and surgery-related factors as well as factors related to the pharmacology of oxycodone were analyzed in association to these oxycodone plasma concentrations.

## RESULTS

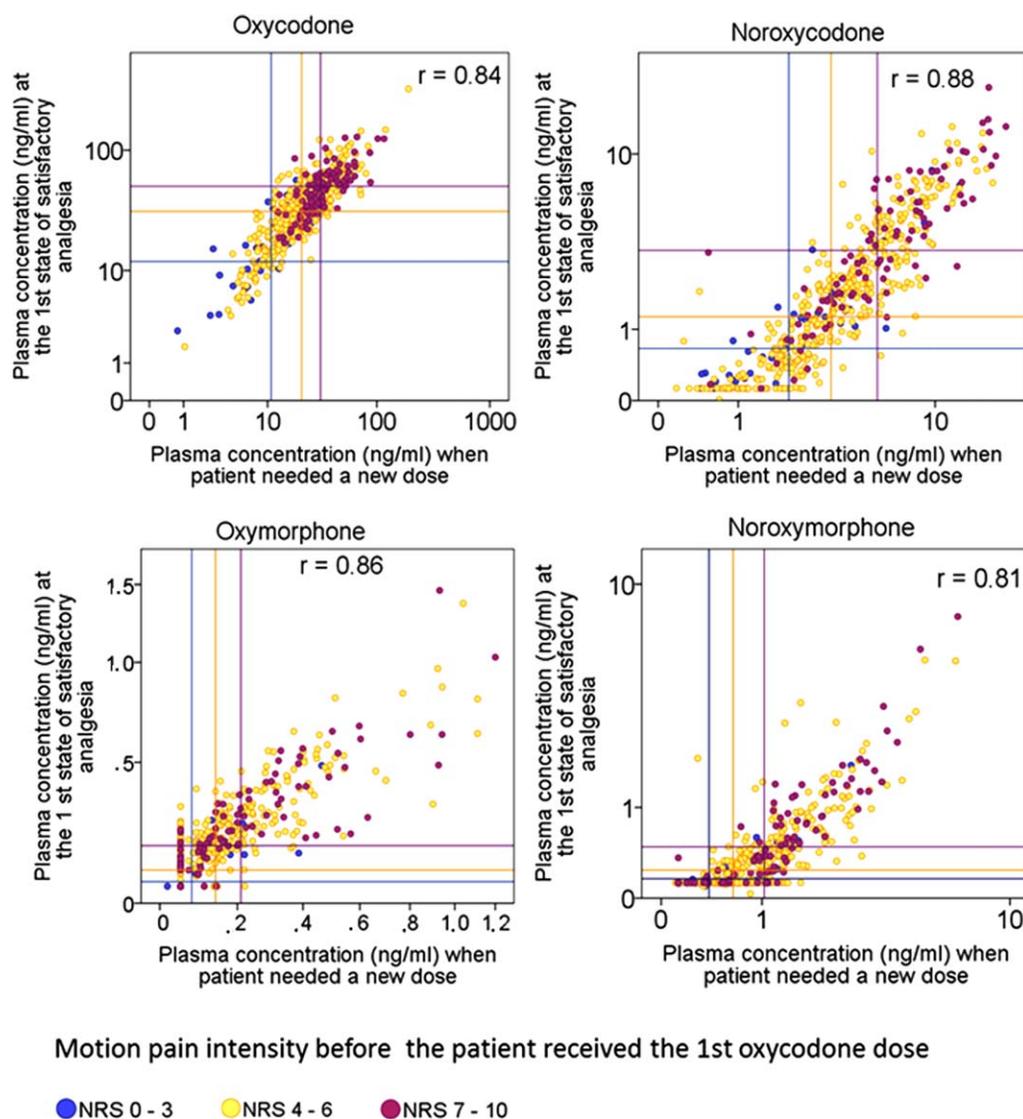
### Oxycodone concentrations at the two time points

Plasma concentrations of oxycodone and its metabolites at the first state of satisfactory analgesia were available from 938 of the 1,000 patients. Three hundred ninety-nine patients did not require further oxycodone after having achieved satisfactory analgesia in the postanesthesia care unit (PACU); therefore, the concentrations were available from 539 patients at the latter time point. Their analgesic oxycodone concentrations did not differ significantly from those of the 399 patients who did not need a new dose of oxycodone after having achieved satisfactory analgesia. The patients who did not request more oxycodone were older (mean 58.8 vs. 55.3 years;  $P < 0.001$ ) and had less anxiety preoperatively ( $P < 0.001$ ) than the 539 patients who requested a new dose after satisfactory analgesia (**Supplementary Table S1** online). Forty-seven patients did not request any oxycodone in the PACU. They were significantly older ( $P < 0.01$ ), shorter ( $P < 0.01$ ), and had significantly less preoperative anxiety ( $P < 0.01$ ) than the other patients (**Supplementary Table S2** online). As they were not given oxycodone, their data could not be used in other analyses. Furthermore, the concentration data at the first state of satisfactory analgesia were missing from 15 patients.

Oxycodone plasma concentrations needed for satisfactory analgesia varied greatly between individuals (range,  $<0.1$ –311 ng/mL). The variation remained high (range,  $<0.1$ –191 ng/mL) at the time point when the patient requested a new dose (i.e., on the average 162 min later). The plasma concentrations of both oxycodone and its metabolites correlated strongly between the two time points (**Figure 2**).

Geometric means and geometric coefficient of variations (CV%) for oxycodone and metabolite plasma concentrations at the first state of satisfactory analgesia were: oxycodone 33.3 ng/mL (66%); noroxycodone 1.46 ng/mL (106%); oxymorphone 0.11 ng/mL (110%), and noroxymorphone 0.26 ng/mL (150%). When the patient requested a new dose, the concentrations were: oxycodone 21.7 ng/mL (69%); noroxycodone 3.67 ng/mL (73%); oxymorphone 0.14 ng/mL (89%); and noroxymorphone 0.67 ng/mL (92%).

The analgesic plasma concentrations of oxycodone correlated significantly with the weight-adjusted total dose of oxycodone needed for the first state of adequate analgesia (**Figure 3**). Yet, the individual concentrations varied up to fourfold after the same weight-adjusted total dose. The individual with the highest oxycodone concentration at both time points also had an exceptionally low dose/concentration ratio. We could not identify any obvious reason for these exceptionally high concentrations. Excluding that patient from the statistical analysis did not change the conclusions.



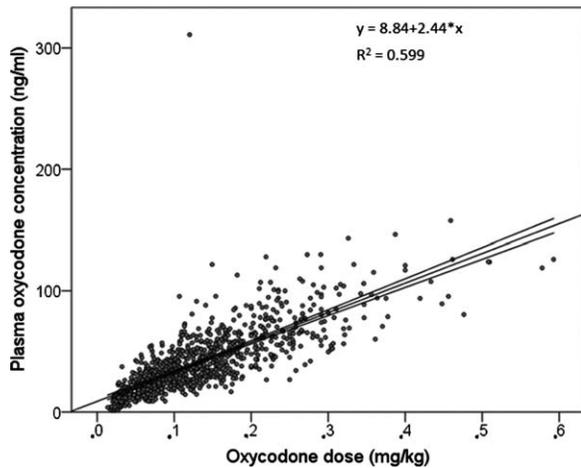
**Figure 2** Correlations between plasma concentrations of oxycodone and its three main metabolites at the two time points: when the patient indicated satisfactory analgesia for the first time (first state of satisfactory analgesia) and when the patient needed a new dose of oxycodone. The patients are divided into three groups based on the intensity of motion pain after surgery before the first dose of oxycodone was administered. The geometric mean of each group is given as a colored line. Numerical rating scale (0–10) of pain intensity.

### Factors affecting analgesic oxycodone concentrations

In a multivariate linear regression analysis, pain intensity after surgery and the type of surgery were strongly associated with the analgesic oxycodone concentration. The analgesic oxycodone concentration increased by 21.7% (95% confidence interval (CI) = 17.5–26.1;  $P < 0.001$ ) per one motion pain intensity score increase on a 0–10 numerical rating scale (NRS; **Table 1**). The 170 patients with high motion pain intensity scores (NRS 7–10) needed nearly twofold higher plasma oxycodone concentrations (geometric mean 50.7 ng/mL) than the 699 patients having moderate pain intensity (NRS 4–6; oxycodone 31.6 ng/mL), and almost threefold higher concentrations than the 59 patients with low postoperative motion pain intensity (NRS 0–3; oxycodone 17.8 ng/mL; **Figure 4**). The mean intravenous oxycodone doses needed for the analgesic concentrations in these three pain score

groups were 0.18 mg/kg, 0.10 mg/kg, and 0.07 mg/kg, respectively (**Table 2**). The motion and rest pain intensities were in almost complete correlation ( $r = 0.99$ ; **Table 1**).

The plasma oxycodone concentration required for satisfactory analgesia was significantly higher (mean, 23.4%; 95% CI = 12.1–36.0%;  $P < 0.001$ ) in those who had removal of the axillary lymph nodes (axillary clearance (AC)) compared to sentinel node biopsy only. In patients having undergone AC, the geometric mean plasma oxycodone concentration was 38.7 ng/mL (66%) and in those having undergone sentinel node biopsy it was 29.6 ng/mL (62%). The corresponding doses of oxycodone needed for these analgesic concentrations were 0.13 mg/kg and 0.10 mg/kg, respectively. The type of breast surgery (breast conserving surgery/mastectomy) had no statistically significant effect on the analgesic oxycodone concentration (**Table 1**). In addition, other



**Figure 3** Correlation between oxycodone doses (mg/kg) and plasma concentrations (ng/mL) during the first state of satisfactory analgesia. A linear regression line with 95% confidence interval is provided.

patient characteristics (e.g, age, smoking, body mass index (BMI), preoperative anxiety, and heat pain or cold pain sensitivity) showed no statistically significant effect on the analgesic plasma concentrations of oxycodone.

**CYP2D6, CYP3A4/5, and OPRM1 genotypes**

The *CYP2D6* metabolizer status could be inferred from the genotype in 918 patients. There were 80 ultrarapid metabolizers (UMs), 799 EMs, 16 intermediate metabolizers (IMs), and 23 PMs. The genotype groups did not differ in regard to the demographic factors. Major differences were seen between the *CYP2D6* genotype groups in the oxymorphone and noroxymorphone concentrations, both when the patients reported satisfactory analgesia for the first time and when they needed a new dose (Table 3). No significant differences were seen in the oxycodone or noroxycodone concentrations between the *CYP2D6* genotypes. *CYP3A4* rs35599367 (\*22 allele) or *CYP3A5* rs776746 (\*3 allele) single nucleotide variations (SNVs) showed no significant effects on oxycodone or its

**Table 1** Factors affecting the plasma oxycodone concentration at the time point when the patient reported satisfactory analgesia for the first time

Variables	B	95% CI		P value
		Lower	Upper	
Motion pain when the patient received the first oxycodone dose (per 1 point on a scale from 0–10)	21.7%	17.5%	26.1%	< 0.001
AC (vs. SNB)	23.4%	12.1%	36.0%	< 0.001
<b>Excluded variables</b>	<b>Beta</b>			<b>P value</b>
Weight, kg	–4.0%			0.21
Lean body weight, kg	–2.4%			0.44
Anxiety (STAI)	2.5%			0.45
Mastectomy	4.0%			0.25
Age, years	–4.3%			0.18
BMI, kg m <sup>–2</sup>	–3.4%			0.28
Pre-operative chronic pain condition	–2.6%			0.43
Pre-operative pain in the breast	5.3%			0.11
Heat pain intensity (NRS)	4.8%			0.15
Cold pain intensity at 30 seconds (NRS)	4.3%			0.20
Time patients kept their hand in ice-cold water, seconds	–3.1%			0.34
Pain at rest when the patient received the first dose of oxycodone (NRS)	27.3%			0.25
Smoking	–1.4%			0.67
<i>OPRM1</i> rs1799971 genotype	1.8%			0.58
<i>CYP2D6</i> genotype <sup>a</sup>	–4.0%			0.21
<i>CYP3A4</i> rs3559967 genotype (*22)	5.7%			0.09
<i>CYP3A5</i> rs776746 genotype (*3)	3.5%			0.29

Results were obtained using forward type linear regression. Excluded variables are phenotypes tested but determined insignificant.

R square for the model is 0.169.

AC, axillary clearance; B, increase in oxycodone concentration needed for satisfactory analgesia; BMI, body mass index; CI, confidence interval; SNB, sentinel node biopsy; STAI, Spielberger State Anxiety Inventory; NRS, numerical rating scale (0–10).

<sup>a</sup>Genotypes were ultrarapid, extensive, intermediate, and poor metabolizers.

**Table 2** Types of surgery and analgesic oxycodone doses and concentrations by pain intensity score groups

	NRS 0–3 (n = 59)	NRS 4–6 (n = 699)	NRS 7–10 (n = 170)
Breast conserving surgery / mastectomy (%)	35 / 24 (59 / 42)	452 / 247 (65 / 35)	91 / 79 (54 / 46)
SNB / AC (%)	38 / 21 (64 / 36)	410 / 289 (59 / 41)	73 / 97 (43 / 57)
Total amount of oxycodone needed by the first state of satisfactory analgesia, mg/kg			
Geometric mean (CV%)	0.07 (73)	0.10 (62)	0.18 (48)
Range	0.01–0.3	0.02–0.6	0.03–0.6
Plasma concentration at the first state of satisfactory analgesia, ng/mL			
Oxycodone			
Geometric mean (CV%)	17.8 (76)	31.6 (66)	50.7 (48)
Range	<2.1–95.4	<0.1–311	9.6–130
Noroxycodone			
Geometric mean (CV%)	0.8 (129)	1.3 (109)	3.3 (76)
Range	<0.3–8.4	<0.3–16.5	<0.3–20
Oxymorphone			
Geometric mean (CV%)	0.1 (97)	0.1 (108)	0.2 (89)
Range	<0.1–0.5	<0.1–1.1	<0.1–1.2
Noroxymorphone			
Geometric mean (CV%)	0.2 (124)	0.2 (144)	0.5 (127)
Range	<0.3–1.8	<0.3–5.2	<0.3–7.6
Plasma concentration when the patient needed a new dose, ng/mL			
Oxycodone			
Geometric mean (CV%)	11.0 (66)	20.9 (69)	31.5 (53)
Range	0.8–38.2	1.1–191	12.7–115.9
Noroxycodone			
Geometric mean (CV%)	2.1 (90)	3.5 (69)	5.6 (62)
Range	0.5–12.6	0.2–17.1	0.5–19.3
Oxymorphone			
Geometric mean (CV%)	0.1 (87)	0.1 (86)	0.2 (80)
Range	<0.1–0.5	<0.1–1.4	<0.1–1.5
Noroxymorphone			
Geometric mean (CV%)	0.4 (93)	0.6 (90)	1.0 (79)
Range	<0.3–2.7	<0.3–6.6	<0.3–6.7

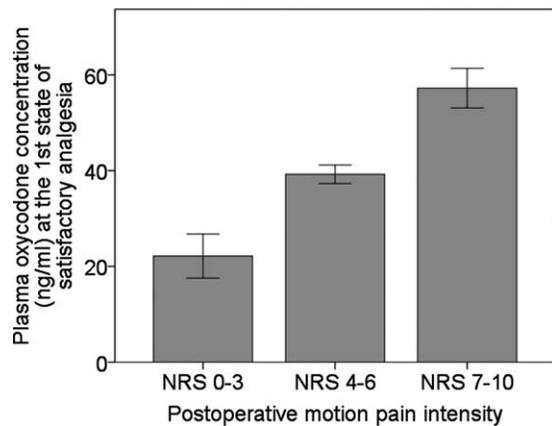
Type of surgery, total amount of oxycodone needed, and the oxycodone and metabolite concentrations at the first state of satisfactory analgesia in the patients who are divided into three groups based on the intensity of motion pain after surgery and before the first dose of oxycodone was administered. Continuous variables are given as geometric means and ranges. Categorical variables are given as the number of patients and percentages.

AC, axillary clearance; CV%, coefficient of variation; NRS, numerical rating scale; SNB, sentinel node biopsy.

metabolite concentrations at either of the two time points. Neither the *CYP2D6* nor the *CYP3A4/5* polymorphisms affected the duration of the analgesic effect (i.e., the time between satisfactory analgesia and the need for a new oxycodone dose). The *OPRM1* c.118A>G genotype did not significantly affect the analgesic plasma oxycodone concentration.

## DISCUSSION

To our knowledge, this is the largest study assessing analgesic oxycodone concentrations and factors affecting these in the immediate postoperative phase. The patient group was homogenous as it consisted of only female patients sharing the same ethnic background (white patients). The study showed that there is wide



**Figure 4** The arithmetic means (SD) of analgesic oxycodone plasma concentrations by postoperative motion pain intensity score groups. NRS, numerical rating scale (0–10).

variation in the analgesic plasma concentrations of oxycodone after breast cancer surgery. The concentration ranged from 0 (i.e., no oxycodone needed) to 311 ng/mL. Postoperative pain intensity and type of axillary surgery were the most important factors associated with the analgesic oxycodone concentration. Axillary surgery was associated with significantly more pain than sentinel biopsy. However, even in the axillary surgery group, some patients did not need any oxycodone in the PACU, whereas some patients required high plasma oxycodone concentrations in the absence of axillary surgery.

#### Type of surgery

The type of surgery that is performed to operate due to breast cancer depends mainly on the cancer status. The patients may need either removal of the breast (mastectomy) or resection of part of it. In addition, sentinel biopsies are performed to confirm the presence or absence of metastasis in the axillary lymph nodes. AC is related to a high risk of nerve injury, which has been reported to be associated with more intense postoperative pain. In accordance with this, AC significantly increased plasma oxycodone concentrations needed for satisfactory analgesia compared to sentinel node biopsy. Evoked postoperative pain is usually more severe than pain at rest. We tested evoked pain by asking the patient to raise the arm ipsilateral to surgery. Even though pain on movement showed the most significant association with analgesic plasma oxycodone concentrations, also pain at rest was a good predictor. As the rest pain was in strong correlation with pain during movement, it was not entered into the linear regression model. When considering the association between type of surgery and analgesic oxycodone concentrations, it can be expected that even higher concentrations than those reported in the current study may be needed after more extensive surgery. In line with this, two recent studies of 50 patients each suggested that the average analgesic concentration after open abdominal surgery would be about 75 ng/mL.<sup>27</sup> Three small studies ( $N = 22-23$ ) have assessed the minimum effective analgesic plasma oxycodone concentrations after laparoscopic cholecystectomies. One reported that the mean analgesic plasma concentration is 45

or 50 ng/mL.<sup>25</sup> The second study suggested that depending on whether 1 g or 2 g of intravenous acetaminophen was co-administered, the analgesic plasma concentration of oxycodone would be 62 ng/mL or 70 ng/mL, respectively.<sup>26</sup> The third study reported that the average analgesic concentration of oxycodone was 98 ng/mL or 80 ng/mL, depending on whether 10 mg or 50 mg of intravenous dexketoprofen was co-administered, respectively.<sup>28</sup> The preoperative analgesic in our study was 1 g acetaminophen orally.

#### Pain sensitivity and anxiety

Anxiety associates with pain sensitivity and fear of pain.<sup>6,29</sup> Anxious patients expect to experience more pain and also report higher pain intensity in experimental pain tests, and in acute and chronic pain. In the current study, anxiety was not independently associated with postoperative analgesic oxycodone concentrations in the multivariate linear regression analysis. This may be partly due to the fact that our patients had, on average, relatively low levels of anxiety. It is also possible that the effects of anxiety on analgesic oxycodone concentration were conveyed through pain intensity scores in the regression analysis. Patients who did not need any oxycodone, or did not need further oxycodone in the PACU after having achieved satisfactory analgesia, had significantly less anxiety than patients who needed additional oxycodone.

#### Age

In the linear regression analysis, age was not significantly associated with the analgesic oxycodone concentration. However, patients who did not need any oxycodone were significantly older than those who did. This agrees with the reports that older patients have less postoperative pain.<sup>30</sup> Similarly, those patients who did not need further oxycodone in the PACU after having achieved satisfactory analgesia were significantly older than those who did. Previously, Kaiko<sup>31</sup> reported higher age to be associated with increased sensitivity to oral oxycodone. The need of lower total doses of oxycodone by elderly patients has been related to a prolonged elimination of oxycodone.<sup>7</sup>

#### Gender, OPRM1, and smoking

All our patients were women. Therefore, the results cannot be generalized to male patients. Kaiko<sup>31</sup> also reported that women are more sensitive to the effects of oral oxycodone than men. We have previously reported in this patient cohort that the *OPRM1* c.118A>G polymorphism explained only 1% of the variance in the oxycodone dose needed for satisfactory analgesia. Only 35 patients were homozygous for the minor allele (GG) and, on average, they needed 30% more oxycodone for satisfactory analgesia.<sup>24</sup> However, in the current analysis, the *OPRM1* c.118A>G polymorphism had no significant effect on the analgesic oxycodone concentration. Nicotine has analgesic effects and abstinent smokers request more opioids in the postoperative period than nonsmokers.<sup>13</sup> In the current study, however, tobacco smoking did not have a significant impact on analgesic oxycodone concentrations. This may be explained by the fact that <20% of the women smoked, and smoking was mostly occasional.

**Table 3 Postoperative oxycodone doses and concentrations by CYP2D6 genotype**

	PM	IM	EM	UM	P value
Total amount of oxycodone needed by the first state of satisfactory analgesia, mg/kg					
Geometric mean (CV%)	0.09 (73)	0.12 (51)	0.11 (66)	0.12 (53)	0.323
Duration of the analgesic effect, min					
Geometric mean (CV%)	85.4 (118)	130.0 (86)	67.3 (121)	62.3 (121)	0.414
Concentration at the first state of satisfactory analgesia, ng/mL					
	PM (n = 23)	IM (n = 16)	EM (n = 799)	UM (n = 80)	
Oxycodone					
Geometric mean (CV%)	28.9 (73)	38.8 (48)	33.0 (67)	40.1 (53)	0.374
Range	5.7–130	14.1–88.1	<0.1–311	10.6–128	
Noroxycodone					
Geometric mean (CV%)	1.0 (112)	2.0 (86)	1.3 (107)	1.8 (92)	0.962
Range	<0.1–8.7	<0.1–11.1	<0.1–20	0.1–13.4	
Oxymorphone					
Geometric mean (CV%)	0.05 (58)	0.06 (68)	0.11 (112)	0.17 (92)	< 0.001
Range	<0.1–0.21	<0.1–0.22	<0.1–1.7	<0.1–1.1	
Noroxymorphone					
Geometric mean (CV%)	0.05 (103)	0.07 (107)	0.17 (168)	0.26 (137)	0.003
Range	<0.1–0.38	<0.1–0.38	<0.1–7.6	<0.1–5.2	
Concentration when the patient needed a new dose, ng/mL					
	PM (n = 17)	IM (n = 4)	EM (n = 448)	UM (n = 52)	
Oxycodone					
Geometric mean (CV%)	17.6 (84)	23.8 (57)	21.6 (70)	24.5 (60)	0.629
Range	6.3–73.3	14.5–47.9	0.77–191.0	7.78–67.3	
Noroxycodone					
Geometric mean (CV%)	3.2 (87)	6.3 (64)	3.7 (73)	3.7 (66)	0.879
Range	0.43–12.6	3.52–13.8	0.17–19.3	0.57–14.2	
Oxymorphone					
Geometric mean (CV%)	0.06 (56)	0.09 (36)	0.14 (88)	0.22 (75)	< 0.001
Range	<0.1–0.18	<0.1–0.13	<0.1–1.46	<0.1–0.97	
Noroxymorphone					
Geometric mean (CV%)	0.06 (68)	0.27 (109)	0.62 (92)	1.02 (81)	< 0.001
Range	<0.1–0.23	<0.1–1.2	<0.1–6.7	<0.1–5.1	

CV%, coefficient of variation; EM, extensive metabolizer; IM, intermediate metabolizer; PM, poor metabolizer; UM, ultrarapid metabolizer.

### Pharmacokinetic factors

Our study was designed to focus on the analgesic oxycodone concentrations after initial titration to adequate pain relief attempting to minimize interference by pharmacokinetic factors. The brain and plasma concentrations of oxycodone have been reported to achieve equilibrium relatively fast compared to morphine. The average transfer half-life from plasma to brain is 11 min for oxycodone,<sup>32</sup> whereas it can vary from 1.6–4.8 h for morphine.<sup>33</sup> This difference may be due to an active transport of oxycodone through the blood-brain barrier into the brain.<sup>34,35</sup> Preclinical studies suggest that the free brain concentrations of

oxycodone could be clearly higher than those in plasma.<sup>36</sup> This would suggest that the brain oxycodone concentrations are not directly commensurate to plasma concentrations, and that differences in the still unidentified transport protein could explain some of the variations in the analgesic plasma concentrations of oxycodone.

*CYP2D6* genotype did not affect the analgesic oxycodone concentrations, but it was associated with metabolite formation. As expected, the concentrations of oxymorphone in the PM and IM patients were about one-third compared with the UM patients. The effect of *CYP2D6* genotype was also evident in the plasma

noroxymorphone concentrations, particularly in the second plasma samples, where the UM patients had nearly 10-fold higher noroxymorphone concentrations than the PM patients. The high (8.7%) frequency of the UM variants among the patients with breast cancer corresponds well with the UM frequency of 7.2% in healthy Finnish subjects.<sup>37</sup> The *CYP2D6* status did not affect the time the patients remained satisfied with analgesia, which would indicate lack of significant analgesic contribution by the metabolites. This is also supported by the fact that when the patients requested a further dose of oxycodone, the oxycodone concentrations had decreased to an average of 21.7 ng/mL from the 33.3 ng/mL at the first state of satisfactory analgesia, whereas the concentrations of the metabolites had risen. The *CYP3A4*\*22 and *CYP3A5*\*3 alleles did not show any significant effect on oxycodone or metabolite concentrations, possibly due to small effects or the low number of minor allele carriers.

### What does analyzing analgesic oxycodone concentrations add to monitoring oxycodone requirements?

As measurement of central nervous system oxycodone concentrations is rarely feasible, plasma oxycodone concentrations should be the most sensitive measure to assess the individual relationship between oxycodone and its analgesic effect. Fast development of equilibrium between central nervous system and plasma concentrations of oxycodone enables rapid titration to the analgesic effect and minimal interference by other pharmacokinetic factors. Thus, several factors of interest relating to the pharmacogenetics and the transporter systems relevant to oxycodone may be studied using analgesic oxycodone concentrations as a “phenotype.”

To conclude, postoperative analgesic plasma oxycodone concentrations varied more than a 100-fold between individuals. The major factors predicting the analgesic oxycodone concentrations were immediate postoperative pain intensity and whether the patient had undergone axillary clearance or not. Estimation of immediate postoperative pain intensity is a clinically useful tool when predicting patient’s oxycodone requirements.

### METHODS

Our study population consisted of 1,000 Finnish women diagnosed with nonmetastasized breast cancer who were to undergo surgery for breast cancer at the Breast Surgery Unit, Helsinki University Hospital, Helsinki, Finland, between August 2006 and December 2010. Exclusion criteria were bilateral or metastasized cancer and immediate breast reconstruction. Of the 1,536 eligible patients, 1,149 were asked to participate in the study. One hundred twenty-six patients declined and 23 were withdrawn due to contraindication to the anesthesia protocol, violation of the study protocol, change in the type of surgery, or for logistic reasons. The study protocol has earlier been described in detail.<sup>5</sup> The age distribution of the patients was:  $\leq 40$  years ( $n = 48$ ); 41–60 years ( $n = 559$ ); and 61–75 years ( $n = 393$ ). Pre-operatively, one patient was taking sublingual buprenorphine and another seven were taking a combination of codeine/acetaminophen or tramadol. Data on concomitant medications affecting the *CYP3A5* and *CYP2D6* pathways are shown in **Supplementary Table S3** online.

The Coordinating Ethics Committee (journal number 136/E0/2006) and the Ethics Committee of the Department of Surgery (148/E6/05) of the Hospital District of Helsinki and Uusimaa, and the Finnish Medicines Agency FIMEA had approved the study protocol. A written informed consent was obtained from each patient. After consent,

demographic, medical, and medication data were collected from all patients. The patients also completed the Beck Depression Inventory<sup>38</sup> and the Spielberger State and Trait Anxiety Inventory<sup>39</sup> questionnaires.

Before surgery, cold and heat pain sensitivities were assessed. In the cold pain sensitivity test, the patient immersed her hand into 40 L of cold (2–4°C) water (Julabo USA, Allenton, PA). Pain intensity was recorded every 15 s using NRS 0–10, zero representing “no pain” and 10 “worst pain imaginable.” The patients were advised to withdraw the hand from the water at any time when the pain felt intolerable. The maximum time was set to 90 s. The time the patients kept the hand in the water was recorded. Heat pain was assessed with a thermode (16 mm  $\times$  16 mm) placed on the volar side of the forearm contralateral to surgery. The thermode (TSA-II, NeuroSensory Analyzee; Medoc Ltd, Ramat Yishai, Israel) was first heated to 43°C (control), and then to 48°C for 5 s. The patients were asked to assess the intensity of pain using NRS 0–10. Cold pain data were available from 900 patients only due to the unavailability of the test device in the beginning of the study.

Surgery was personalized according to the patient’s wishes and the clinical characteristics of the tumor. Anesthesia was standardized. All patients were premedicated with peroral diazepam 2.5–15 mg and acetaminophen 1 g. A venous blood sample was drawn for DNA analysis at the induction of anesthesia, which consisted of intravenous propofol and remifentanyl. Before moving to the PACU, all patients were given fentanyl (1  $\mu$ g/kg i.v.), ondansetron (4 mg i.v.), and dehydrobenzperidol (0.01 mg/kg i.v.). In the PACU, the patients were immediately asked to assess their pain intensity during rest and motion before the first oxycodone dose. Motion pain was tested by asking the patient to raise her arm 90° ipsilateral to the surgery. The research nurse asked the patients about rest and motion pain intensity every 5 min and administered them with 1–3 mg i.v. oxycodone if they reported NRS  $\geq 3$ . This was repeated until the patient indicated satisfactory analgesia, and the first blood sample for oxycodone and its metabolite determination was taken at this point. After this, the pain scores were recorded every 15 min until the patient required a new dose. At this time point, the time from the previous administration was recorded and the second blood sample was taken before the new dose was administered. After about 2.5 h in the PACU, the patients were given a patient-controlled analgesia device and were moved to the surgical ward.

### DNA extraction and genotyping

DNA was extracted from peripheral blood using the Autopure LS automated DNA purification instrument (Gentra Systems, Minneapolis, MN). All genotyping was done blindly to phenotype information. Patients were genotyped for 10 *CYP2D6* SNVs and copy number variations using Taqman genotyping assays and a copy number assay targeting exon 9.<sup>37</sup> *CYP2D6* metabolizer groups were inferred from the genotype data using the activity score method.<sup>40</sup> *CYP3A4* rs35599367 (\*22) was genotyped with a commercially available kit (C\_59013445\_10) and the *CYP3A5* rs776746 (\*3) was assessed with a custom Taqman genotyping assay.<sup>41</sup> Sequenom MassARRAY and iPLEX Gold Single Base Extension chemistry (Sequenom, San Diego, CA) were used to genotype *OPRM1* rs1799971. Results were confirmed using duplicates and positive and negative control samples in each DNA plate.

### Measurement of oxycodone and its metabolites

Plasma concentrations of oxycodone and three of its metabolites were quantified using an API 3000 liquid chromatography-tandem mass spectrometry system (Sciex Division of MDS, Toronto, Ontario, Canada), as described previously, from 0.5 mL plasma samples (see **Supplementary Data S1**).<sup>42</sup> The method was validated according to the US Food and Drug Administration guidelines.<sup>43</sup> The lower limits of quantification for oxycodone and oxymorphone, and noroxycodone and noroxymorphone were 0.1 ng/mL and 0.25 ng/mL, respectively. Interday coefficient of variation was below 15% for all analytes at relevant concentrations.

### Statistical analysis

The data were analyzed using SPSS Statistics version 22 (IBM, Armonk, NY). Oxycodone and its metabolite concentrations below the limit of quantification were replaced with half of the quantification limit, except for those patients who did not need any oxycodone and were excluded from the respective analyses. Oxycodone and its metabolite concentrations were logarithmically transformed before statistical analysis. Possible effects of the variables affecting plasma oxycodone concentrations were investigated using a stepwise, forward linear regression analysis. The tested variables included age, height, weight, lean body weight, BMI, smoking status, preoperative anxiety, preoperative chronic pain condition, preoperative pain in the breast, *OPRM1*, *CYP2D6*, and *CYP3A4* genotypes, surgery type (mastectomy/breast conserving, and sentinel node biopsy/AC), preoperative cold and heat pain sensitivities, cold pain tolerance, and postoperative rest and motion pain intensities. Statistical significance level was set at  $P < 0.05$  for entry into the model and  $> 0.10$  for removal. Possible effects of *CYP2D6* genotypes on oxycodone metabolite concentrations were investigated with one-way analysis of variance, as were the differences between postoperative pain intensity groups. The results are expressed as geometric means with geometric CV% or relative effects with 95% CIs. Possible correlations of oxycodone and its metabolite concentrations between the two studied time points were investigated with the Pearson correlation coefficient. The differences between the 47 patients who did not require any oxycodone, and the rest of the patients were investigated using independent sample *t*-test for the continuous variables, Fisher's exact test for the surgery type, and Pearson's  $\chi^2$  for *OPRM1* genotype. Same statistical tests were also used to determine differences between the 539 patients who required additional oxycodone in the PACU after first satisfactory analgesia, and the 399 who did not. The  $P$  values  $< 0.05$  were considered statistically significant.

**SUPPLEMENTARY MATERIAL** is linked to the online version of the article at <http://www.cpt-journal.com>

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### CONFLICT OF INTEREST

The authors declared no conflict of interest.

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### AUTHOR CONTRIBUTIONS

K.C. and M.N. wrote the manuscript. E.K., M.A.K., P.J.N., and M.N. designed the research. M.N. and O.K. performed the research. K.C. and M.N. analyzed the data.

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