

No significant influence of OCT1 genotypes on the pharmacokinetics of morphine in adult surgical patients

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Abstract

We investigated the impact of genetic variants in *OCT1* (*SLC22A1*) on morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) pharmacokinetics in adult patients scheduled for major surgery. Blood samples were taken before and 5, 10, 15, 30, 45, 60 and 90 min after a bolus of morphine (0.15 mg/kg). Patients were genotyped for the genetic variants (rs12208357, rs34059508, rs72552763 and rs34130495) in *OCT1*.

Eighty-six patients completed the trial. The mean difference (95% confidence interval) for dose adjusted morphine, M3G and M6G AUC was 0.9 (−0.7–2.4), −5.9 (−11.8 to −0.03) and −1.1 (−2.5–0.4) h/L*10^{−6}, respectively, in patients with two reduced function alleles compared to patients with no reduced function alleles in *OCT1*. Accordingly, the (AUC_{M3G/Dose})/(AUC_{morphine/Dose}) and (AUC_{M6G/Dose})/(AUC_{morphine/Dose}) ratio was reduced, −1.8 (−3.2 to −0.4) and −0.4 (−0.7 to −0.03), respectively, when comparing the same groups. *OCT1* variants had no influence on the experience of pain, adverse events or the number of PCA doses used. In conclusion, genetic variants in *OCT1* had a small and clinically unimportant impact on the exposure of morphine after intravenous administration. Our results do not support pre-emptive

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genotyping for *OCT1* prior to morphine administration in patients scheduled for major surgery.

KEYWORDS

M6G, morphine, organic cation transporter 1, pharmacodynamics, pharmacokinetics

1 | INTRODUCTION

Morphine is the most widely prescribed opioid to treat severe acute and chronic pain.¹ It is well known that patients show substantial interindividual variability in the response and therefore also in the required dose of morphine.¹ A multitude of factors such as sex and organ function may explain some of the variability; however, genetic variants in enzymes and transporters that affect morphine pharmacokinetics may also contribute.²

Following an intravenous (i.v.) bolus, morphine is rapidly distributed to highly perfused organs such as the liver and kidneys.¹ The *OCT1* transporter (encoded by *SLC22A1*), which is expressed in the basolateral membrane of hepatocytes,³ facilitates >65% of the hepatic uptake of morphine following clinically relevant doses of the drug.⁴ *OCT1* is highly polymorphic, and four common genetic variants in the gene (rs12208357, rs34059508, rs72552763 and rs34130495) that results in reduced cellular uptake of morphine have been found in Caucasians.^{4,5} About 10% of Caucasians carry two reduced function (rf) *OCT1* alleles,⁶ which might impact the pharmacokinetics of morphine and its metabolites, potentially with clinical implications. It was recently demonstrated that the hepatic uptake of the active metabolite of another opioid, tramadol, *O*-desmethyltramadol, which is transported by *OCT1* is decreased in patients and infants with two rf alleles compared with those carrying one or none rf alleles.^{7,8} Patients with two rf alleles also showed reduced post-operative tramadol consumption compared to those carrying one or none rf alleles.⁸ Whether the same reduction in opioid use is true for morphine is not known and the impact of genetic variants in *OCT1* on the pharmacokinetics of morphine is inconsistent across studies. Both in vitro and clinical studies have reported an impact of *OCT1* polymorphism on the pharmacokinetics of morphine,^{4,9–11} though data are not consistent.^{12,13}

Morphine undergoes extensive hepatic metabolism. The major metabolic pathway is glucuronidation that is predominantly catalysed by uridine 5'-diphosphoglucuronosyltransferase 2B7 (UGT2B7) into the inactive morphine-3-glucuronide (M3G) (55%) and the analgesic active morphine-6-glucuronide (M6G) (15%).^{1,14} Both

morphine and M6G crosses the blood–brain barrier where they exert their effect primarily on the μ -opioid receptor.¹⁵ Approximately 10% of the morphine dose is excreted unchanged in the urine.^{15,16}

The main purpose of the present study was to evaluate the impact of *OCT1* genotypes on morphine, M6G and M3G exposure by comparing diplotypes (none, one, or two rf alleles) in adult patients undergoing major surgery. We hypothesized that in individuals with two rf *OCT1* alleles, morphine transport will be slower, resulting in higher systemic exposure. We exploratively studied the potential effect on pain-free period after major surgery.

2 | METHODS

2.1 | Study participants

Patients planned for elective laparoscopic colon or rectum resection surgery at Odense University Hospital or the Hospital Southwest Jutland in Esbjerg were eligible. Inclusion criteria were American Society of Anesthesiology classification, (ASA) I–III,¹⁷ body mass index (BMI) below 35 kg/m² age 18–90 years and Caucasian descent. Exclusion criteria were regional anaesthesia during surgery or for post-operative pain management, intake of opioids on a regular basis, alcoholism, contraindication to the use of morphine, other serious conditions (terminal cancer, severe heart, lung or liver disease, renal failure, severe dementia or mental illness), pregnant or breastfeeding women and women in the childbearing age not using safe contraceptives. Written informed consent was obtained from patients meeting the inclusion criteria who wished to participate.

2.2 | Study design

This was an open-label study. All participants were planned to receive standard perioperative care with a standard anaesthetic at the discretion of the anaesthesiologist in charge. Briefly, patients fasted minimum 6 h before surgery. In the morning of the surgery, patients

received their daily medication with few possible exceptions such as oral anticoagulants and angiotensin-converting enzyme (ACE) inhibitors. Anaesthesia was induced with i.v. injections of propofol (2–2.5 mg/kg), sufentanil (~0.25 µg/kg) and rocuronium (0.6–1 mg/kg). The anaesthesia was maintained with desflurane (minimum alveolar concentration [MAC] 0.8–1.3) and refractory doses of sufentanil and rocuronium, guided by neuromuscular block monitoring. Under normal circumstances, patients would receive the anti-emetic drug ondansetron. Since this drug is known to inhibit the OCT1 transporter,^{18,19} dexamethasone was used instead as this is not expected to inhibit the transporter.

Approximately 30 min before termination of surgery, patients received the interventional single dose of i.v. morphine hydrochloride (HCl) 0.15 mg/kg (0.13 mg/kg free base). An arterial catheter was placed, and blood sampling for pharmacokinetic analyses was performed before and 5, 10, 15, 30, 45, 60 and 90 min after drug administration.

2.3 | Post-operative analgetic treatment

The analgesic regimen in the recovery ward consisted of acetaminophen 1000 mg × 4/day and subsequent patient-controlled analgesia (PCA) until 24 h after the first morphine bolus (the end of the study period). The PCA device was set to a bolus dose of i.v. morphine 0.04 mg/kg and a lockout time of 8 min. Patients undergoing surgery would normally receive morphine as part of the analgesic regimen, however, not as PCA. The patients rated their pain at rest and during activation at arrival at the recovery ward, 60 min, 90 min and 4, 8, 12 and 24 h after the first morphine bolus. Pain was rated on a 10-point numerical rating scale (NRS) on which 0 represents *no pain at all* and 10 represents *the most pain imaginable*. Additionally, the patients rated the severity of itching and nausea on a 4-point NRS at 4, 8, 12 and 24 h after the first morphine bolus. In case of patients' wish for rescue medication, the normal procedure for pain treatment in the department was followed. Patient records were investigated 24 h after the first morphine bolus in order to detect any adverse reactions described by the ward physician but not picked up by the questionnaire or use of other pain medication than the PCA pump and acetaminophen.

2.4 | Study procedures

The study was approved by the Danish Medicines Agency (EudraCT nr.: 2017-004946-25), OPEN at the

University of Southern Denmark (no: OP_510) and approved by the Regional Committees on Health Research Ethics for Southern Denmark (J. no: S-20170221) and the Danish Data Protection Agency (J. no. 2012-58-0018). The trial was registered at www.clinicaltrials.gov (NCT03425084). The study was conducted in accordance with the Helsinki Declaration and Good Clinical Practice, and monitored by the Good Clinical Practice unit, Odense University Hospital, Odense, Denmark. Further, the study was conducted in accordance with the *Basic & Clinical Pharmacology & Toxicology* policy for experimental and clinical studies.²⁰

2.5 | Analytical methods

The plasma concentration of morphine, M3G and M6G were determined at the Department of Public Health, Clinical Pharmacology, Pharmacy and Environmental Medicine, University of Southern Denmark, using isotope dilution and liquid chromatography and tandem mass spectrometry (LC-MS/MS). The method has previously been described in detail.²¹ Briefly, blood samples were collected in BD Vacutainers blood collection tubes with EDTA as anticoagulant (BD, Franklin Lakes, NJ, USA). Blood was centrifuged at 3000 × g for 10 min, and plasma was stored at –20°C until drug analysis. The within-batch precision (CV%) was ~ < 8% for morphine and M6G and ~ < 6.5% for M3G. The between-batch precision (CV%) was ~ < 9% for M6G, ~ < 4% for M3G and ~ < 11% for morphine. The lower limit of quantification was 0.2 ng/ml for morphine, M3G and M6G.

2.6 | Genotyping

Genomic DNA was extracted from an aliquot of venous blood using the Maxwell 16 Blood DNA Purification Kit (Promega Corporation, Madison, WI, USA). Selected single nucleotide polymorphisms (SNPs) in OCT1 (rs12208357; rs34059508; rs72552763; rs34130495) were genotyped as previously described.²² Briefly, rs72552763 (M420del) and rs34130495 (G401S) were genotyped by Sanger sequencing. The rs12208357 (R61C) and rs34059508 (G465R) were genotyped using predesigned TaqMan SNP genotyping assays on a StepOne Plus real-time instrument (Applied Biosystems, Thermo Fisher Scientific, Foster City, CA, USA) according to the manufacturer's protocol. Assay numbers and sequence of primer and probes used for genotyping are summarized in Table S1.

2.7 | Statistical analysis and considerations

Data distribution of all investigated parameters was evaluated using QQ plots. The descriptive and pharmacodynamic data are presented as medians with 25th and 75th percentile range (IQR). Patients missing more than one out of four answers on the drug adverse events questionnaire and two out of seven answers on the pain questionnaire were excluded from the statistical analysis post hoc. Patients who used other pain medication than acetaminophen and/or PCA were excluded from statistical analysis concerning pain scores: NRS area under the curve (AUC_{0-24h}), adverse-effect scores NRS AUC_{4-24h} and number of PCA uses. If patients had used the other pain medication before the first PCA dose, they were also excluded from the statistical analyses concerning the time after surgery to first PCA dose. Multiple linear regression adjusted for sex, BMI, total morphine use (mg) and age was used to investigate *OCT1* diplotypes impact (wt/wt vs. wt/rf vs. rf/rf and rf/rf vs. [wt/rf + wt/wt]) on pain scores AUC_{0-24h} and adverse-effect scores AUC_{4-24h} . T0 is equal to the arrival at the recovery ward as this equals the first time the patients are asked to evaluate their pain score. Multiple linear regression adjusted for age, sex, and BMI was also used to investigate the impact of *OCT1* diplotypes on the time that passed after surgery to first PCA, the total number of PCA uses and PCA uses in each time interval. Before statistical analysis, visually guided by QQ plots, the time that passed after surgery to first PCA dose was logarithm-transformed to approximate a Gaussian distribution. Wilcoxon rank-sum test was used to evaluate the number of PCA uses among men and women.

The AUC of morphine, M3G and M6G were normalized by the size of the first bolus dose of morphine hydrochloride as it differed among patients. Pharmacokinetic data are presented as means with standard deviation. The mean difference between diplotypes with a 95% confidence interval was calculated using a non-paired *t*-test. All statistical analyses were performed using Stata Statistical Software: Release 16 (StataCorp LP, College Station, TX, USA).

2.8 | Pharmacokinetics

All pharmacokinetic parameters were calculated by non-compartmental methods using the software package 'NCAPPC' in R, Version 3.6.3. The area under the plasma concentration–time curves of morphine, M6G and M3G were calculated using the linear-up log-down trapezoidal method. The actual blood collection times

were used for determination of all morphine, M6G and M3G parameters.

2.9 | Diplotype inference

The diplotypes of the four loss-of-function alleles in *OCT1* were inferred using the software package PHASE, Version 2.1.1 (University of Washington, Seattle, WA, USA) by Stephens et al.²³ The program was run multiple times with random seeds in order to evaluate the robustness of the inferred haplotypes.

2.10 | Sample size

We conservatively assumed that the expected difference in AUC (or clearance) of morphine is between 20% and 50%^{4,9} and that the coefficient of variation is about 40%.^{4,8} Assuming a wt/wt and wt/rf (or rf/rf) distribution of 50% among included patients, a true 25% difference in AUC can be detected with inclusion of 90 patients while allowing for a 10% patient dropout, with a power of 80% and a significance level of 0.05.

3 | RESULTS

In total, 98 patients consented to participate; however, due to consent withdrawal, use of other pain medication, technical issues with devices and blood sampling and missing questionnaire answers, a reduced number of patients were eligible for the different analyses. For each analysis, we used the largest possible number of eligible patients as presented in the flow chart (Figure 1). Demographics of the included patients can be found in Table 1.

The distribution of haplotypes *s* in *OCT1*, [c.181 (C > T) rs12208357; c.1201 (G > A) rs34130495; c.1260 (GAT > del) rs72552763; c.1393 (G > A) rs34059508] is listed in Table S2, and the distribution of diplotypes are presented in Table 2. The impact of diplotypes (wt/wt vs. wt/rf and wt/wt vs. rf/rf) on the pharmacokinetics of morphine, M3G and M6G is listed in Table 3 and in Figure 2, while the impact of having none or one rf allele compared to two rf alleles ([wt/wt + wt/v] vs. v/v) on morphine pharmacokinetics is presented in Table S3.

There was a trend towards an increase in the mean $AUC_{morphine(0-1.5h)} / Dose$ in patients carrying rf alleles in *OCT1* with a concomitant drop in $AUC_{M3G(0-1.5h)} / Dose$ and $AUC_{M6G(0-1.5h)} / Dose$ (Table 3). The $AUC_{morphine(0-1.5h)} / Dose$ was ~20% higher in patients carrying two rf alleles compared to those carrying none. The confidence interval limits just barely included zero

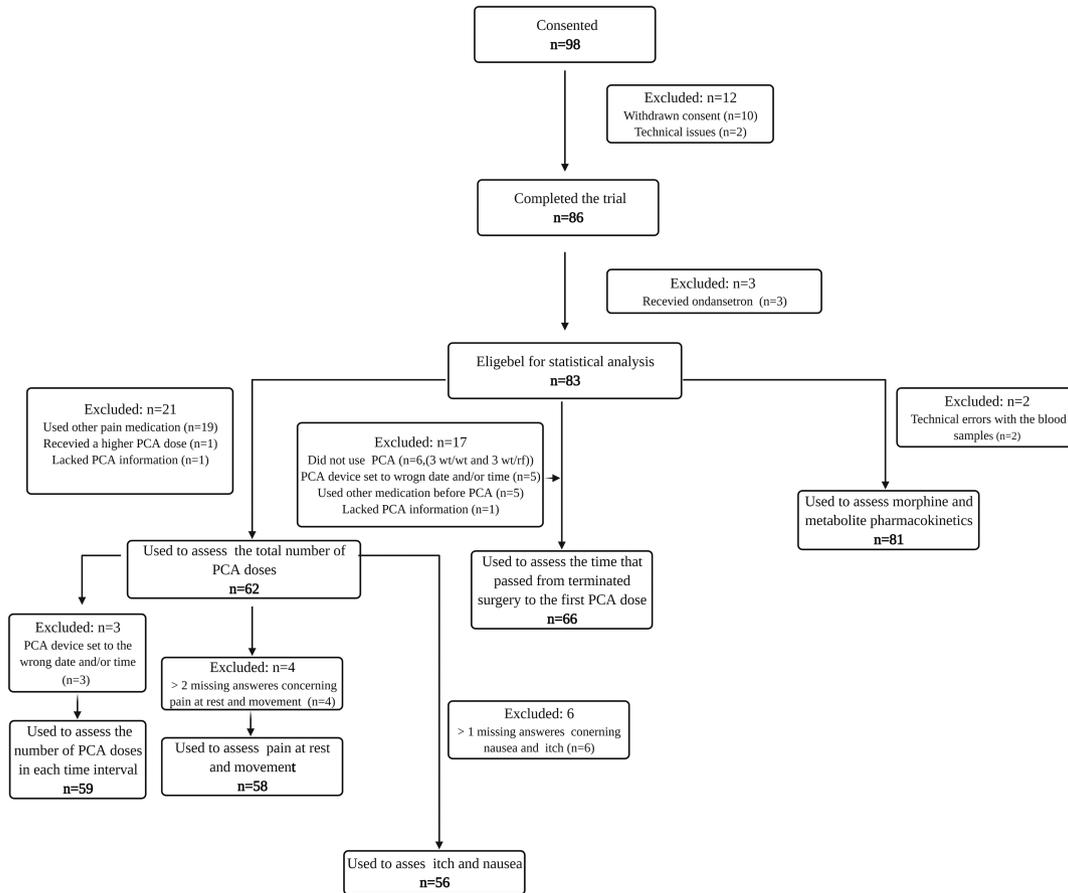


FIGURE 1 Overview of the number of patients included in each statistical analysis

TABLE 1 Demographic information

Demographic information	Median	25th–75th percentile
Age (years)	70	64–75
Weight (kg)	78	64–92
Height (m)	1.70	1.70–1.80
BMI (kg/m ²)	25	23–29

Note: Sex: female 34, male 52.

in this parameter with a central tendency suggesting an increase ($p = 0.3$). The decrease in $AUC_{M3G(0-1.5h)}/Dose$ and $AUC_{M6G(0-1.5h)}/Dose$ was $\sim 20\%$ and 15% , respectively. The confidence limits did not include the null in $AUC_{M3G(0-1.5h)}/Dose$ parameter and just barely included null for $AUC_{M6G}/Dose$ with a central tendency suggesting a reduction ($p = 0.05$ and 0.2 , respectively). These results were consistent when comparing patients carrying two rf alleles with those carrying one or none ([wt/wt] + wt/rf vs. rf/rf) (Table S3).

The mean $(AUC_{M3G}/Dose)/(AUC_{morphine}/Dose)$ and $(AUC_{M6G}/Dose)/(AUC_{morphine}/Dose)$ ratio was

significantly decreased in patients with two rf alleles compared with patients carrying none rf alleles (rf/rf vs. wt/wt) (Table 3) and the same applied for $(AUC_{M3G}/Dose)/(AUC_{morphine}/Dose)$ when comparing patients with one or none rf alleles with those carrying two rf alleles ([wt/wt + wt/rf] vs. rf/rf) (Table S3).

None of the patients experienced any serious adverse events. The total morphine consumption was associated with pain scores during rest and movement ($p < 0.01$) as well as the adverse event itching ($p = 0.003$) but not nausea ($p = 0.4$). The *OCT1* diplotypes did not affect NRS $AUC_{movement0-24h}$, $AUC_{rest0-24h}$, $AUC_{nausea4-24h}$ or $AUC_{itch4-24h}$ ($p > 0.05$). The same applied when investigating patients with a fully answered questionnaire (not missing a single answer) ($p > 0.05$) and patients with one or none rf alleles with those carrying two rf alleles ($p > 0.05$). For further details, see Table S4.

The patients' sex and BMI were associated with the number of PCA doses ($p = 0.001$ and $p = 0.04$, respectively). Males used more PCA doses 11 (5–16) (25th–75th interquartile range) than females 7 (4–9) ($p = 0.02$). The *OCT1* diplotypes did not have a statistically significant impact on the total number of PCA doses (respectively,

TABLE 2 The distribution of *OCT1* genotypes in 86 patients

Haplotypes ^a	C.181C > T	c. 1201G > A	c.1260GAT > del	c.1393G > A
H1	C	G	GAT	G
H2	C	G	del	G
H3	C	G	del	A
H4	C	A	GAT	G
H5	T	G	GAT	G
Diploypes for RF in <i>OCT1</i> ^b	<i>n</i>	Diploypes		
H1/H1	35	WT/WT [<i>n</i> = 35 (41%)]		
H1/H2	17			
H1/H3	7			
H1/H4	8	WT/RF [<i>n</i> = 43 (50%)]		
H1/H5	11			
H2/H3	1			
H2/H4	2			
H2/H5	1	RF/RF [<i>n</i> = 8 (9%)]		
H3/H3	1			
H3/H5	1			
H4/H5	2			

Note: The minor alleles are shown in grey

Abbreviations: Del, deletion; n, number of patients/diploypes, WT, wild type, the haplotype with only active alleles.

^aHaplotypes for RF *OCT1* (the haplotypes consist of rs12208357, rs34059508, rs72552763, rs34130495).

^bDiploypes for reduced function (RF) *OCT1*.

TABLE 3 Impact of *OCT1* reduced function diploypes on morphine pharmacokinetics

	wt/wt <i>N</i> = 32 mean (SD)	wt/rf <i>N</i> = 42 mean (SD)	Mean difference (95% CI) wt/wt vs. wt/rf	rf/rf <i>N</i> = 7 mean (SD)	Mean difference (95% CI) wt/wt vs. rf/rf
AUC _{morphine(0-1.5h)} /Dose (h/L*10 ⁻⁶)	5.3 (1.7)	5.5 (2.0)	0.2 (-0.7-1.1)	6.2 (2.5)	0.9 (-0.7-2.4)
AUC _{M3G(0-1.5h)} / Dose (h/L*10 ⁻⁶)	28.4 (7.1)	28.3 (7.5)	-0.1 (-3.6-3.3)	22.5 (6.2)	-5.9 (-11.8 - -0.03)
AUC _{M6G(0-1.5h)} / Dose (h/L*10 ⁻⁶)	7.0 (1.7)	6.7 (1.8)	-0.2 (-1.1-0.6)	5.9 (1.8)	-1.1 (-2.5-0.4)
(AUC _{M3G/Dose})/ (AUC _{morphine/Dose})	5.7 (1.8)	5.5 (1.6)	-0.2 (-1.0-0.6)	3.9 (1.0)	-1.8 (-3.2 - -0.4)
(AUC _{M6G/Dose})/ (AUC _{morphine/Dose})	1.4 (0.4)	1.3 (0.4)	-0.1 (-0.3-0.1)	1.0 (0.3)	-0.4 (-0.7 - -0.03)

Notes: Impact of *OCT1* reduced function diploypes (rf) diploypes on morphine and metabolites AUC adjusted for full dose and metabolite/parent drug ratio adjusted for full dose. Data are presented as means with standard deviations and the difference as means with a 95% confidence interval.

Abbreviations: RF, reduced function; WT; wild type.

wt/wt, wt/rf, rf/rf; 8.5 [3.0-12.0], 7 [4-12] and 12 [9-18]) or the number of PCA doses in the four time intervals ($p > 0.05$) (Figure 3). Accordingly, there was no statistical difference in the total number of PCA doses or the number of PCA doses used in each time interval when comparing patients with one or none rf alleles with those carrying two rf alleles ($p > 0.05$).

The *OCT1* diploype did not affect the time interval that passed after surgery to first PCA bolus (respectively, wt/wt, wt/rf, rf/rf; 3 h [2-4 h], 2 h [1-3 h] and 2 h [1-2 h]) ($p > 0.05$). The same applied when comparing patients carrying one or none rf alleles with those carrying two rf alleles (wt/wt + wt/rf vs rf/rf) ($p = 0.4$).

FIGURE 2 The median unadjusted plasma concentration of morphine, M3G and M6G in 81 patients

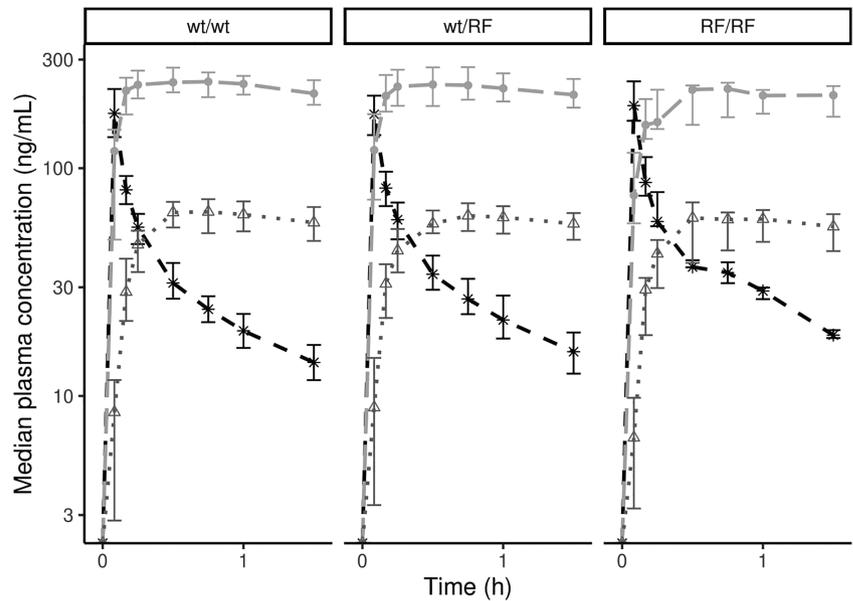
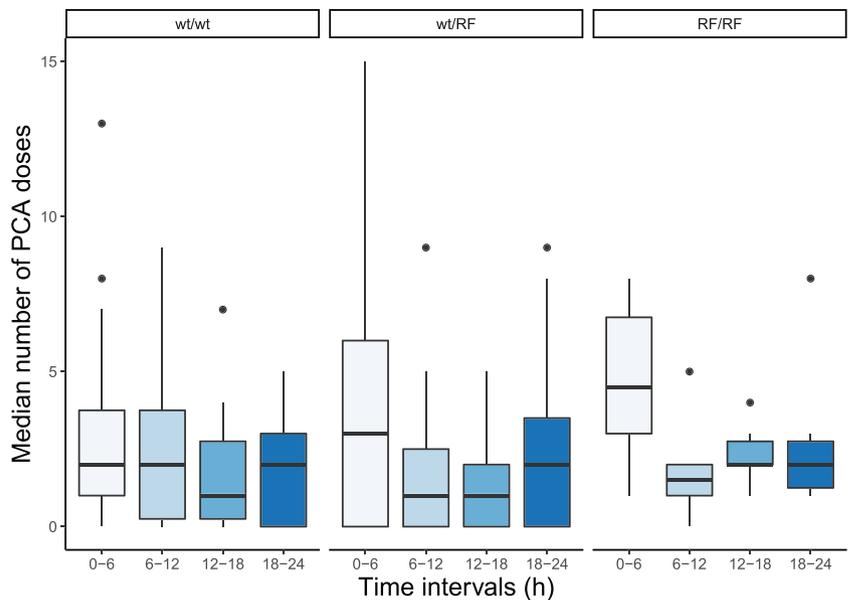


FIGURE 3 The median (25th–75th IQR) number of PCA doses used for each genotype in different time intervals. The whiskers represents the third quartile + (1.5*IQR) and the first quartile – (1.5*IQR). Dots beyond this are presented as outliers



4 | DISCUSSION

This is the largest pharmacokinetic study investigating the impact of genetic variants in *OCT1* on the pharmacokinetics of morphine in adult patients. The study demonstrates that common genetic variants in *OCT1* have a small impact on the exposure of morphine and its primary metabolites following i.v. administration.

In vitro studies have presented strong evidence that rf alleles in the *OCT1* results in reduced cellular uptake of morphine.⁴ In accordance, the exposure of morphine increases by almost 50% in healthy volunteers carrying two rf alleles compared to those carrying one or two active alleles in *OCT1* following intake of the prodrug

codeine.⁴ In that study, the increase in morphine exposure was greater than what we observed; however, the number of included individuals was only 25, that is, considerably less than in our study and only two individuals carried two rf alleles in *OCT1*. We used i.v. morphine in our trial, and whether the administration of the active drug instead of a prodrug could impact the importance of genetic variants on the exposure of morphine is not known but seems unlikely. Reduced function in *OCT1* has not been demonstrated to affect the pharmacokinetics of morphine, M3G and M6G following an oral administration.^{12,13} This could possibly be due to masked effects of the genotype by interindividual variance in the bioavailability of the drug. Genetic variants in *OCT1* have

been reported to reduce the clearance of morphine in 220 children following i.v. morphine,¹⁰ while no effect was detected on the total clearance of morphine or the morphine metabolic clearances to M3G and M6G in adult cancer patients following subcutaneous injection.¹³

Our results indicate that genetic variants in *OCT1* have a small effect on the pharmacokinetics of morphine, M3G and M6G (~15%–20% change in AUC). While not excluding a null finding for morphine and M6G, the 95% confidence interval just barely including zero, indicating that it is more likely that there is a true difference between the groups than that there is no difference. We hypothesize that the increase in morphine exposure with concomitant lower exposure of plasma M3G and M6G in patients carrying two rf alleles is a result of slower uptake of morphine into the liver. Minor changes in the plasma concentration of morphine may have an impact on the effect and risk of adverse events as placebo-controlled trials have reported an increased risk of adverse events in *CYP2D6* normal but not in poor metabolizers after codeine intake, due to higher plasma levels of morphine.²⁴ High age and female sex are known risk factors for experiencing morphine-related adverse events,²⁵ and the impact of genetic variants in *OCT1* on the risk of adverse events might be greater in these patients.

A limitation in this study is the relatively short time interval where blood samples were taken. Hence, morphine's AUC was not extrapolated to infinity as the median percentage of extrapolated AUC was 26% range (9–67). The fact that blood samples were only collected for 90 min after drug administration may exclude some important information about morphine elimination. A longer blood sample interval would not be possible as patients are in pain after the surgery and require morphine. This is also why five patients only had blood samples taken until 60 min after morphine injection. Theoretically, we could have given another pain rescue medication that did not interfere with the *OCT1* transporter and extended the blood sampling time. That would, however, result in us being unable to compare pain and adverse events scores and the number of PCA doses of morphine used. Another limitation is that we did not have any information on the patients' daily medication. Hence, we cannot rule out drug–drug interactions at transporters responsible for morphine disposition which theoretically could have an impact on morphine pharmacokinetics and therefore affect our results. Furthermore, the surgical staff estimated when there was half an hour left of the surgery. In some cases, this estimation turned out to be wrong meaning that some patients had received sufentanil after the first morphine bolus which theoretically could have an impact on pain scores in the first hours after surgery. The impact is,

however, expected to be low as sufentanil only provides sufficient analgesia for a short period of time.

In contrast to a previous study demonstrating that patients with rf alleles used less tramadol,⁸ we saw no such associations with the number of morphine PCA doses in this study ($p > 0.05$) (Figure 2). Males used a higher number of PCA doses than females ($p = 0.03$). In accordance, a systemic review and meta-analysis based on human experimental and clinical studies have previously concluded that women are more sensitive to morphine,²⁶ although this is not univocal as other studies cannot demonstrate a difference in morphine pharmacodynamics between sexes.^{27,28} Pain is an individual and unpleasant experience that apart from biological factors can be influenced by physiological and social factors.²⁹ Genetic variants in transporters of antinociceptive drugs may therefore only contribute to the interindividual experience of pain following major surgery. It is important to recognize that this study cannot rule out a contribution of genetic variants on the experience of pain, adverse events or the total use of PCA doses as the study was not powered to detect pharmacodynamic changes and several patients did use other pain medication than acetaminophen or PCA and had to be excluded from the statistical analysis.

As expected, there were no difference in the experience of adverse events between the genetic variants ($p > 0.05$) as patients self-medicated through PCA and could therefore control the amount of morphine entering the body.

5 | CONCLUSION

Genetic variants in *OCT1* seem to have a small impact on the exposure of morphine, M3G and M6G following an i.v. bolus of morphine. Patients carrying two loss-of-function alleles in *OCT1* had a ~20% increase in dose-adjusted morphine AUC with a concomitant ~20% decrease in dose-adjusted M3G and M6G AUC compared to patients carrying no loss-of-function alleles. Furthermore, a decrease in dose-adjusted metabolite/parent drug ratio for both M3G and M6G was observed in patients carrying two loss-of-function alleles. This impact is unlikely to be of clinical importance. *OCT1* variants had no influence on the experience of pain, adverse events or the number of PCA doses used. Our findings do not support pre-emptive genotyping for *OCT1* before morphine treatment.

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CONFLICT OF INTEREST

The authors declare no conflict of interest associated with this manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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