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ORIGINAL ARTICLE

Opioid-related genetic polymorphisms do not influence postoperative opioid requirement

A prospective observational study

Frédéric Aubrun, Noël Zahr, Olivier Langeron, Nicolas Boccheciampe, Nathalie Cozic, Lisa Belin, Jean-Sebastien Hulot, Frederic Khiami and Bruno Riou

BACKGROUND Among the various factors that may influence the pharmacological response to opioids, genetic polymorphisms [single nucleotide polymorphisms (SNP)] have generated some interest.

OBJECTIVES To examine the influence on morphine dose requirements and adverse events in the postoperative period of four SNP [opioid receptor mu1 (OPRM1), ATP-binding cassette subfamily B, member 1 (ABCB1) ex-21 and ex-26, catechol-o-methyltransferase (COMT)] in candidate genes involved in morphine pharmacodynamics and pharmacokinetics.

DESIGN A single centre prospective study.

SETTING University Hospital, Paris, France, from 2 January 2007 to 15 November 2011.

PATIENTS A total of 438 white adults scheduled for major orthopaedic surgery (spine, hip and knee) under general anaesthesia. The main exclusion criteria were receiving opioids for chronic pain, nonopioid drugs within 2 days prior to surgery, pregnancy, renal insufficiency, sleep apnoea obstruction syndrome, morbid obesity, severe hepatic impairment, cognitive dysfunction.

INTERVENTIONS Assays of plasma concentrations of morphine and metabolites (morphine 3-glucuronide and morphine 6-glucuronide) were performed and common polymorphisms in four candidate genes [*OPRM1* A118G rs1799971; P-glycoprotein (*ABCB1*) T3435C (rs1045642) and G2677T/A (rs2032582); *COMT* Val 158 Met (rs4680)] were analysed.

Morphine was titrated by staff in the postanesthesia care unit (PACU) and in the ward patient-controlled intravenous analgesia was used for 24 h.

MAIN OUTCOME MEASURES The dose of morphine required to achieve pain relief and the influence of SNP in genes involved in morphine pharmacodynamics and kinetics on morphine dose requirements. Secondary endpoints were the concentrations of morphine, morphine 6-glucuronide and morphine 3-glucuronide, the proportion of patients requiring a rescue analgesic and the proportion of morphine-related adverse events.

RESULTS A total of 404 patients completed the study to final analysis. The mean \pm SD morphine dose to achieve pain relief was 15.8 ± 8.8 mg in the PACU and 22.7 ± 18.6 mg during patient-controlled intravenous administration. Morphine-related adverse events were observed in 37%. There was no relationship between any genetic polymorphisms and morphine dose, morphine 3-glucuronide and morphine 6-glucuronide concentration, morphine-related adverse events or pain level. In the PACU only, P-glycoprotein polymorphisms (ex-21; ex-26) were significantly associated with morphine concentration but the prediction of the model was poor ($R^2 = 0.04$)

CONCLUSION No major relationship has been demonstrated between SNP of *OPRM1*, *ABCB1*, *COMT* and morphine requirement, pain level or adverse effects in the postoperative period.

TRIAL REGISTRATION NCT00822549 (www.clinicaltrials.gov).

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Introduction

Postoperative pain control remains a clinical challenge for the anaesthesiologist and opiate analgesics are the drugs most widely used to treat moderate and severe postoperative pain.¹ The two main principles of postoperative pain control are first, self-assessment of pain by the patient and second, titration of the analgesic treatment according to its effect.^{1–4} However, there is considerable interindividual variability in pain intensity and the pharmacological response to analgesic treatment, including opioids. This interindividual variability concerns both the dose and concentrations needed (efficacy) and adverse effects (safety).^{1,5} Although opioids are considered to be the most potent analgesics available they may also be associated with severe adverse events.³

Among the various factors that may influence opioid treatment, genetic polymorphisms have generated some interest. So far, four main single nucleotide polymorphisms (SNP) have been studied. The opioid receptor mu 1 (*OPRM1*) gene encodes for the μ -opioid receptor, a G protein-coupled receptor, which mediates the analgesic effects of morphine in the central nervous system. The A118G (Asn40Asp) polymorphism of *OPRM1* has been associated with an altered pharmacodynamic response to morphine and morphine 6-glucuronide (the main metabolite of morphine), including analgesic effects and adverse events.^{2,6} P-glycoprotein (P-gp), multidrug resistance 1 or, ATP-binding cassette subfamily B, member 1 (*ABCB1*), a drug efflux transporter, is considered to be a major component of the blood–brain barrier and can limit morphine disposition in the central nervous system.^{7,8} Two main polymorphisms in exon 21 and exon 26 are observed in *ABCB1* gene. Catechol-*o*-methyltransferase (*COMT*) metabolises catecholamines and several studies suggest there are links between dopaminergic and adrenergic systems and pain transmission. Also a common polymorphism (p.Val158Met) leads to reduced activity, explaining part of the interindividual difference in the adaptation and response to pain; it may affect morphine dosing requirements and adverse events.^{9,10} Several studies have investigated the role of genetic variation in morphine pharmacodynamics and the pharmacokinetics.¹¹ If the concept of individualised care, based on identification of intrinsic and environmental influences on pharmacological responses, is to move forward, then this topic may be important, but to date no clear clinical conclusion has been reached.¹²

The aim of this study was to examine the role of four genetic polymorphisms (*OPRM1*, *ABCB1* ex-21 and ex-26, *COMT*) in candidate genes potentially involved in morphine pharmacodynamics and pharmacokinetics in patients undergoing major orthopaedic surgery. We separately assessed two postoperative periods, the early postoperative period in the postanesthesia care unit (PACU) where intravenous morphine was titrated, and

the late postoperative period in the surgical ward where patient-controlled intravenous administration (PCA) morphine was given for 24 h. It is known clinically that these two periods markedly differ when considering the dose and concentration of morphine required for pain relief and the role of patient characteristics such as age.¹³ We tested the hypothesis that these genetic polymorphisms influenced the dose of morphine required.

Methods

The current prospective study was approved by Comité de Protection des Personnes (No. CPP27-06 CPP de Paris – Ile de France VI, Groupe Hospitalier Pitié Salpêtrière Paris, France) on 12 April 2006, and was carried out between the 2 January 2007 and 15 November 2011. All patients provided informed written consent. The study was conducted according to Good Clinical Practice standards and the Helsinki Declaration. The study has been registered (NCT00822549).

Patient characteristics

The criteria for inclusion in the study were age 18 years or greater, white origins, ASA classification 1 to 3, and scheduled orthopaedic surgery with predictable moderate to severe postoperative pain (spine, hip and knee surgery). The investigators verified that patients were able to understand and follow the protocol, including the visual analogue pain scale (VAS). The exclusion criteria included the following: ASA classification 4 to 5, any chronic pain medication as opioids, nonopioid or nonsteroidal anti-inflammatory drugs or corticosteroids within 2 days prior to surgery; pregnancy, age under 18 years, current or past drug use, refusal to consent, renal insufficiency (estimated creatinine clearance $<30 \text{ ml min}^{-1}$ using the Cockcroft formula), sleep apnoea obstruction syndrome, morbid obesity ($\text{BMI} > 35 \text{ kg m}^{-2}$), severe hepatic impairment, cognitive dysfunction or known allergies or contra-indication to morphine or paracetamol. Patients requiring emergency surgery or regional anaesthesia and patients with hepatic insufficiency were excluded. Those with a contraindication to droperidol (known or suspected long QT syndrome or hypersensitivity to the drug) were also excluded.

Study design

This was a single centre prospective study. Patients were recruited to the study during the pre-operative appointment with the anaesthesiologist (at least 48 h before surgery). The following data were recorded: patient characteristics, including age, sex, BMI, personal history and medical treatment, ASA class. A pregnancy test was performed in women of childbearing age. Pre-operative biological measurements included haemoglobin, creatinine, liver enzymes, platelets counts, prothrombin and partial activated thromboplastin time.

Patients received the following standard care. Premedication consisted of 50 or 100-mg oral hydroxyzine given the previous evening and 1 h before surgery. Anaesthesia was provided using intravenous propofol and sufentanil. Patients were mechanically ventilated with a mixture of nitrous oxide and oxygen (50/50) and sevoflurane. Orotracheal intubation was facilitated by the administration of atracurium (0.5 mg kg^{-1}). Thirty minutes before the end of surgery, all patients received 1 g of intravenous paracetamol and 1.25-mg droperidol, as part of prevention of postoperative nausea and vomiting. After ascertaining the Apfel score for postoperative nausea and vomiting risk, we used our hospital protocol to guide the administration of intravenous dexamethasone at the induction of general anaesthesia (4 to 8 mg) and additional droperidol (1.25 mg) at the end of surgery with 4 mg of ondansetron if required. Patients were extubated in the operating room and then transferred to the PACU where they stayed for at least 2 h, after which they were transferred to the surgical ward. Intra-operatively, we recorded the total dose of all intravenous anaesthetic drugs used, the maximum concentration of sevoflurane and nitrous oxide, and the duration of surgery and anaesthesia.

Postoperative pain management

All nurses in the PACU had been trained to assess pain intensity using unidimensional scales such as the VAS (0 to 100, handheld slide rule type). Postoperative pain management was standardised. Our hospital protocol guided the treatment of acute postoperative pain as follows: 1 g of intravenous paracetamol every 6 h during the first 24 h. A strict protocol of intravenous morphine titration was implemented in the PACU after a previous study had determined the optimal regimen.^{1–4} This protocol defined the dose of intravenous boluses of morphine, the interval between boluses, the absence of a limit on the total dose, the VAS score threshold required to administer morphine, and the criteria to stop titration. After arrival in the PACU when the patients were awake, they were questioned as to the presence of pain (at least every 15 min before the onset of morphine titration) and asked to rate pain intensity on a scale (VAS). When the VAS score was greater than 30, intravenous morphine was titrated every 5 min in 3-mg increments (2 mg in patients weighing $\leq 60 \text{ kg}$), and pain was assessed every 5 min until relief was obtained, defined as a VAS score of 30 or less. Sleeping patients were not disturbed and were considered as having relief from pain; a score of 0 was assigned.² When pain was too severe to obtain a VAS score (patient refusal), it was scored as 100. All patients received oxygen (31 min^{-1}), and clinical monitoring included measurement of respiratory rate, oxygen saturation measured by pulse oximetry, sedation according to the Ramsay score,^{2,14} arterial blood pressure and heart rate. Morphine titration was stopped if the patient had a respiratory rate lower than 12 bpm, oxygen saturation lower than 95%, or had experienced a serious

adverse event related to morphine administration (allergy with cutaneous rash and/or hypotension, vomiting, severe pruritus). In case of severe respiratory depression (respiratory rate $< 10 \text{ bpm}$), naloxone (intravenous bolus of 0.04 mg) was administered until the respiratory rate was greater than 12 bpm. Patients with a VAS score 30 or less did not receive morphine. Morphine titration was interrupted following the occurrence of severe morphine adverse effects. Sedation was considered as a severe morphine adverse effect, as previously reported.^{1–5} Patients could receive other analgesics (or regional anaesthesia) as a rescue procedure in the event of lack of pain relief with morphine. This decision was taken by the anaesthesiologist, usually in patients requiring more than 10 boluses of morphine.

In the surgical ward, pain scores were assessed every hour for the first 4 h and then every 2 h until 24 h after the end of surgery. Pain management included systematic administration of i.v. paracetamol every 6 h and intravenous morphine by PCA (morphine concentration: 1 mg ml^{-1} , bolus dose = 1 mg, lockout time 7 min and no dose limit).

Nausea, vomiting, anti-emetic requirements, sedation and respiratory scores and other adverse events including cardiovascular events, delirium and agitation were recorded.

Details of *Morphine, morphine metabolite and sufentanil measurements* and *Genotyping* can be found in the Supplementary digital material, <http://links.lww.com/EJA/A142> (SPD).

End-points

Two separate analyses were planned, the first in the PACU (early postoperative period with intravenous morphine titration), and the second in the surgical ward (late postoperative period with PCA morphine), as these two periods differed markedly with regard to the dose of morphine required and the influence of its metabolism and related variables.^{3,4} The main end-point was the dose of morphine required to achieve pain relief (VAS score ≤ 30), and we aimed to study the influence on morphine dose requirements of SNP in genes involved in morphine pharmacodynamics and pharmacokinetics. The secondary efficacy endpoints were the concentrations of morphine, morphine 6-glucuronide (M6G) and morphine 3-glucuronide (M3G), and the proportion of patients requiring a rescue analgesic. The secondary safety end-point was the proportion of morphine-related adverse events.

Statistical analysis

The goal was to identify polymorphism of at least one gene of the four studied in relationship to pain relief by intravenous morphine. In the absence of appropriate data to calculate the number of patients required, we estimated the number of patients needed to assess the relationship between SNP of four genes and the morphine dose needed to achieve pain relief in the PACU.

The power of the study required was 80% and the power to detect an effect of each gene was about 96%. Five hundred patients were required to detect a difference of a morphine dose of 0.05 mg kg⁻¹ (30% of the efficient dose), assuming an alpha risk of 0.05 and a beta risk of 0.20 (Nquery Advisor; Statistical Solutions Ltd, Cork, Ireland).

Data are expressed as mean ± SD for normally distributed variables or median and 25th to 75th quartiles (time delay, duration, morphine doses, morphine and morphine metabolites) for nonnormally distributed variables (Shapiro test). Linear analyses were performed to study the impact of different factors on dose and concentration of morphine, M3G and M6G, separately in both PACU and the surgical ward. Age, sex, BMI, ASA class, pain score at arrival in the PACU, previous surgery, sufentanil dose, pre-operative morphine use, pre-operative analgesic use and the four genes with all their SNP tested were examined through univariate analyses. All significant factors at a 10% level after univariate tests were then introduced into a multivariate model. Final models contained factors that survived a stepwise selection but genetic variables were forced into multivariable models as this was the main hypothesis tested. The normality of residuals was checked in all multivariate models. When the normal assumption was not verified a square or log transformation was applied. We calculated the coefficients of regression and their 95% confidence interval (CI). Univariate logistic analysis was used to test whether each previous factor was predictive for the presence of morphine-related adverse effect for each patient. This analysis was also performed separately in each period, in the PACU and on the surgical ward. The same process as above was used to obtain final multivariable models. We calculated the odds ratio (OR) and its 95% CI. Hosmer and Lemeshow's tests were performed to check the calibration of logistic models. Sensitivity analyses were also performed by excluding patients who required rescue analgesic and those who did not require morphine titration in the PACU to test whether these exclusions could change conclusions. All *P* values were two-tailed and a *P* value of less than 0.05 was considered significant. SAS V9.2 (SAS Institute, Cary, North Carolina, USA) was used to perform the statistical analysis.

Results

Of 438 patients assessed for eligibility, 404 patients were retained for the final analysis (SPD Fig. 1, <http://links.lww.com/EJA/A142>). The study was interrupted by difficulties in recruitment. Patient characteristics are shown in Table 1.

Pain management in the postanaesthesia care unit

Median VAS score on arrival in PACU was 70 (80 to 100). Morphine was titrated in 358 (89%) patients with a mean time of 25 (20 to 35) min to reach VAS score 30 or less. The

Table 1 Patient clinical characteristics

Variable	Number of patients	Value
Age	404	60 ± 14
Age >75 years	404	55 (14%)
Men		198 (49%)
Women		206 (51%)
BMI (kg m ⁻²)	402	25.3 ± 3.7
ASA classification	404	
1		195 (48%)
2		191 (47%)
3		18 (4%)
Creatinine clearance (ml min ⁻¹)	388	89 ± 28
Creatinine clearance <60 ml min ⁻¹		56 (14%)
Previous surgery	404	
All surgery		345 (85%)
Surgery with severe postoperative pain		215 (53%)
Preoperative analgesics	404	
Non opioid		114 (28%)
Opioid		35 (9%)
Type of surgery	404	
Hip arthroplasty		262 (65%)
Knee arthroplasty		5 (1%)
Spine surgery		137 (34%)
Expected postoperative pain	404	
Moderate		283 (70%)
Severe		121 (30%)
Duration of surgery (min)	404	114 ± 53
Duration of anaesthesia (min)	404	187 ± 62
Propofol dose (mg)	398	189 ± 76
Sevoflurane concentration (%)	368	1.4 ± 0.5
Nitrous oxide concentration (%)	364	49 ± 4
Sufentanil dose (µg kg ⁻¹)	403	0.59 ± 0.18
Sufentanil dose >0.6 µg kg ⁻¹	403	159 (39%)
Atracurium dose (mg)	402	50 ± 17
Initial VAS	370	71 ± 21
Initial VAS > 60	370	282 (76%)

Data are mean ± SD or number (%) of patients. VAS, visual analogue pain scale.

mean morphine dose required in the PACU to achieve pain relief was 15.7 ± 8.8 mg (0.22 ± 0.12 mg kg⁻¹). There was no significant change in cardiovascular variables (data not shown). There was failure of the morphine titration to achieve a VAS score < 30 in 97 (24%), and thus, additional analgesics were required. Ketamine was the preferred addition to the morphine regimen in the PACU (*n*=94, 97% of patients requiring rescue analgesia). Morphine-related adverse events were observed in 161 (47%) patients (SPD, <http://links.lww.com/EJA/A142>). Table 2 depicts the concentrations of morphine, M3G and M6G at the end of intravenous morphine titration. The concentration of sufentanil was determined in only 41 patients and was 0.10 (0.10 to 0.10) ng ml⁻¹. No significant relationship was observed between intra-operative sufentanil dose and immediate postoperative morphine consumption in the PACU (data not shown). There was no significant relationship between SNP and pain scales, morphine dose and ketamine administration (data not shown).

Pain management in the wards

The mean dose of morphine administered by PCA on the ward was 22.7 ± 18.6 mg (0.31 ± 0.25 mg kg⁻¹). The total

Table 2 Morphine and morphine metabolites concentrations in the postanaesthesia care unit and in the surgical ward

Variable	Number of patients	Value
Morphine (ng ml ⁻¹)		
PACU	338	38 (17 to 69)
Ward	320	6 (2 to 15)
M3G (ng ml ⁻¹)		
PACU	357	282 (121 to 507)
Ward	337	72 (33 to 144)
M6G (ng ml ⁻¹)		
PACU	353	41 (20 to 78)
Ward	335	12 (6 to 28)
Morphine/M3G		
PACU	337	0.12 (0.06 to 0.27)
Ward	320	0.08 (0.04 to 0.23)
Morphine/M6G		
PACU	336	0.79 (0.45 to 1.95)
Ward	318	0.47 (0.21 to 1.00)
M3G/M6G		
PACU	352	6.8 (4.1 to 10.5)
Ward	334	6.5 (2.9 to 10.9)

Data are median (25th to 75th quartiles). M3G, morphine 3-glucuronide; M6G, morphine 6-glucuronide; PACU, postanaesthesia care unit.

combined dose of morphine in the PACU and on the ward over 24 h was 38.2 ± 22.3 mg (0.54 ± 0.31 mg kg⁻¹). Additional analgesics were required to produce pain relief in 13 (3%) patients. Morphine-related adverse events were observed in 158 (44%) patients. Table 2 depicts the concentration of morphine, M3G and M6G at the end of the study period. The concentration of sufentanil was determined in only 30 patients and was 0.10 (0.10 to 0.10) ng ml⁻¹.

Genetic analysis

Frequencies of allelic polymorphisms of *OPRM1*, *ABCB1* and *COMT* are shown in Table 3.

Factors associated with morphine consumption

Only the initial VAS was significantly associated with the morphine requirement during the intravenous titration in

Table 3 Frequency of polymorphism (all single nucleotide polymorphisms were in Hardy-Weinberg equilibrium) (n=404)

	Genotype	Allelic frequency
OPRM1:c.A118>G	G/G	17 (4%)
Missing data: n=14	A/G	89 (22%)
G allele frequency 16%	A/A	284 (70%)
P-gp ex 21	T/T	78 (19%)
Missing data: n=19	G/T	173 (43%)
T allele frequency 44%	G/G	119 (29%)
A allele frequency 2%	G/A	9 (2%)
	A/T	6 (2%)
	A/A	0 (0%)
P-gp ex 26 C3435T	T/T	115 (28%)
Missing data: n=14	C/T	187 (46%)
C allele frequency 47%	C/C	88 (22%)
COMT Val158Met	G/G	116 (29%)
Missing data: n=12	A/G	194 (48%)
A allele frequency 47%	A/A	82 (20%)

Data are number (percentage). COMT, catechol-o-methyltransferase; OPRM1, opioid receptor mu1; P-gp, P-glycoprotein.

the PACU, whereas polymorphisms of *OPRM1*, *ABCB1* and *COMT* were not (Table 4). BMI and the morphine/M6G ratio were associated with morphine dose in the PACU. In the ward, for those using PCA, only the initial VAS, age, and the dose of peroperative sufentanil were significantly associated with the dose of morphine required during the intravenous titration, whereas polymorphisms of *OPRM1*, *ABCB1* and *COMT* were not (Table 5). We conducted a sensitivity analysis (n=298) by excluding patients who required a rescue analgesic, and either in the PACU or in the ward, polymorphisms of *OPRM1*, *ABCB1* and *COMT* remained NS in the multi-variable analyses (data not shown). The sensitivity analysis (n=46) that excluded patients who did not require morphine titration in the PACU also provided comparable results (data not shown).

Factors associated with morphine concentration

In the PACU, both *ABCB1* polymorphisms (exon 21 and 26) were significantly associated with the concentration of morphine but the prediction of the model was poor as shown by the low value of R² (Table 4). In the ward, no variable was significantly associated with the concentration of morphine (Table 5). When considering M3G or M6G, either in the PACU or in the ward, polymorphisms of *OPRM1*, *ABCB1* and *COMT* were non significant in the multivariable analyses (data not shown).

Factors associated with morphine-related adverse event

The sex, initial VAS and ASA score were significantly associated with the occurrence of morphine-related adverse event during the intravenous titration in the PACU, whereas polymorphisms of *OPRM1*, *ABCB1* and *COMT* were not (Table 6). In the ward, only the sex and ASA score were significantly associated with the occurrence of morphine-related adverse events, whereas polymorphisms of *OPRM1*, *ABCB1* and *COMT* were not (Table 6).

Discussion

In white patients undergoing major orthopedic surgery, we studied the role of four genetic polymorphisms (*OPRM1*, *ABCB1* ex-21 and ex-26, *COMT*), involved in opioid pharmacokinetic and pharmacodynamics. However, our study failed to identify clinically relevant data that could demonstrate that these genetic polymorphisms might influence morphine efficacy and safety.

Beside characteristics such as sex and age,^{4,5} genetic factors can alter pain sensitivity and pharmacological responses to opioids.^{7,8} Associations of SNP with increased or decreased pain or modified effects of analgesics have demonstrated that pain therapy is subject to pharmacogenetic differences.^{10,15} Several studies have investigated the impact of *OPRM1* A118 G polymorphism on the requirements and efficacy of intravenous

Table 4 Multivariable analysis predicting morphine dose (primary endpoint) and morphine concentration in the postanaesthesia care unit

Variables	Regression coefficient (95% CI)	P value
Prediction of morphine dose ($n=297$), $R^2 = 0.19$		
Initial VAS > 60	0.09 (0.06 to 0.12)	<0.001
BMI > 25 kg m ⁻²	-0.04 (-0.07 to -0.02)	<0.001
Morphine/M6G	-0.004 (-0.01 to -0.001)	0.01
OPRM1:c.A118>G A/A	0	-
OPRM1:c.A118>G A/G or G/G	0.005 (-0.02 to 0.03)	0.69
P-gp ex 21 G/G	0	-
P-gp A/T or G/T or T/T or G/A or T/A or T/G or A/G	-0.01 (-0.05 to 0.02)	0.38
P-gp ex 26 G/G	0	-
P-gp ex 26 C/T or T/T	0.02 (-0.02 to 0.05)	0.33
COMT Val158Met G/G	0	-
COMT Val158Met A/G or A/A	-0.01 (-0.03 to 0.02)	0.70
Prediction of morphine concentration ($n=299$), $R^2 = 0.04^a$		
Initial VAS > 60	0.12 (-0.01 to 0.25)	0.08
OPRM1:c.A118>G A/A	0	-
OPRM1:c.A118>G A/G or G/G	0.08 (-0.05 to 0.20)	0.23
P-gp ex 21 G/G	0	-
P-gp A/T or G/T or T/T or G/A or T/A or T/G or A/G	-0.16 (-0.32 to -0.01)	0.036
P-gp ex 26 G/G	0	-
P-gp ex 26 C/T or T/T	0.24 (0.08 to 0.41)	0.004
COMT Val158Met G/G	0	-
COMT Val158Met A/G or A/A	0.06 (-0.06 to 0.18)	0.32

CI, confidence interval; COMT, catechol-o-methyltransferase; M6G, morphine 6-glucuronide; OPRM1, opioid receptor mu1; P-gp, P-glycoprotein; VAS, visual analogue pain scale. ^aWe applied a log10 transformation of morphine concentration.

morphine in the postoperative setting.^{16–21} Chou *et al.*²² demonstrated that morphine consumption over the first 24-h postoperative period was higher in women homozygous for the 118G allele compared with women homozygous for the wild-type A118 allele. The incidence of vomiting was more frequent in patients of the AA and AG groups compared with patients in the GG group.²² In contrast, in patients undergoing laparoscopic abdominal surgery, Janicki *et al.*²³ did not observe any significant

association between *OPRM1* A118G polymorphism and the average postoperative pain score and doses of morphine. In a meta-analysis of 23 studies investigating the role of *OPRM1* 118A>G genetic variant in pain management with opioids, Walter and Lötsch²⁴ reported that pharmacogenetic effects had only a minor impact in the clinical setting of pain management. At best, slight protection from nausea and possibly a slight increase in opioid requirements might be expected for homozygous

Table 5 Multivariable analysis predicting morphine dose (primary endpoint) and morphine concentration in the surgical ward

Variables	Regression coefficient (95% CI)	P value
Prediction of morphine dose ($n=348$), $R^2 = 0.12^a$		
Initial VAS > 60	0.09 (0.03 to 0.14)	0.001
Age ≥ 75 years	-0.17 (-0.24 to -0.11)	<0.001
Dose of sufentanil $\geq 0.6 \mu\text{g kg}^{-1}$	0.06 (0.01 to 0.11)	0.02
OPRM1:c.A118>G A/A	0	-
OPRM1:c.A118>G A/G or G/G	0.02 (-0.03 to 0.07)	0.40
P-gp ex 21 G/G	0	-
P-gp A/T or G/T or T/T or G/A or T/A or T/G or A/G	-0.05 (-0.11 to 0.01)	0.12
P-gp ex 26 G/G	0	-
P-gp ex 26 C/T or T/T	0.01 (-0.05 to 0.08)	0.69
COMT Val158Met G/G	0	-
COMT Val158Met A/G or A/A	-0.02 (-0.06 to 0.03)	0.53
Prediction of morphine concentration ($n=305$), ^b $R^2 = 0.01$		
OPRM1:c.A118>G A/A	0	-
OPRM1:c.A118>G A/G or G/G	0.04 (-0.12 to 0.20)	0.59
P-gp ex 21 G/G	0	-
P-gp A/T or G/T or T/T or G/A or T/A or T/G or A/G	0.15 (-0.04 to 0.35)	0.12
P-gp ex 26 G/G	0	-
P-gp ex 26 C/T or T/T	-0.16 (-0.37 to 0.05)	0.15
COMT Val158Met G/G	0	-
COMT Val158Met A/G or A/A	-0.06 (-0.21 to 0.09)	0.43

CI, confidence interval; COMT, catechol-o-methyltransferase; OPRM1, opioid receptor mu1; P-gp, P-glycoprotein. ^aWe applied a square transformation of morphine dose. ^bWe applied a log transformation of morphine concentration.

Table 6 Multivariable analysis predicting morphine-related adverse events in the postanaesthesia care unit and in the surgical ward

Variables	Odds ratio (95% CI)	P value
Prediction of MRAE in the PACU ($n=350$; HL $P=0.78$)		
ASA 1	1	
ASA 2	1.75 (1.00 to 3.06)	0.049
ASA 3	0.23 (0.08 to 0.63)	0.004
Men	1	
Women	1.41 (1.13 to 1.77)	0.003
Initial VAS < 60	1	
Initial VAS \geq 60	1.36 (1.04 to 1.76)	0.02
OPRM1:c.A118>G A/A	1	
OPRM1:c.A118>G A/G or G/G	1.00 (0.78 to 1.30)	0.98
P-gp ex 21 G/G	1	
P-gp A/T or G/T or T/T or G/A or T/A or T/G or A/G	0.78 (0.57 to 1.08)	0.13
P-gp ex 26 G/G	1	
P-gp ex 26 C/T or T/T	0.98 (0.69 to 1.39)	0.91
COMT Val158Met G/G	1	
COMT Val158Met A/G or A/A	1.06 (0.83 to 1.36)	0.62
Prediction of MRAE in the surgical ward ($n=367$; HL $P=0.35$)		
ASA 1	1	
ASA 2	1.78 (1.03 to 3.06)	0.039
ASA 3	0.23 (0.08 to 0.60)	0.003
Men	1	
Women	1.42 (1.15 to 1.75)	0.001
OPRM1:c.A118>G A/A	1	
OPRM1:c.A118>G A/G or G/G	0.99 (0.78 to 1.26)	0.96
P-gp ex 21 G/G	1	
P-gp A/T or G/T or T/T or G/A or T/A or T/G or A/G	0.81 (0.60 to 1.09)	0.16
P-gp ex 26 G/G	1	
P-gp ex 26 C/T or T/T	0.97 (0.70 to 1.34)	0.87
COMT Val158Met G/G	0	
COMT Val158Met A/G or A/A	1.03 (0.82 to 1.30)	0.77

CI, confidence interval; COMT, catechol-o-methyltransferase; HL, Hosmer–Lemeshow; MRAE, morphine-related adverse event; OPRM1; opioid receptor mu1; PACU; postanaesthesia care unit; P-gp, P-glycoprotein; VAS; visual analogue pain scale.

carriers.²⁴ We failed to identify clinically relevant data that could demonstrate that *OPRM1* polymorphisms might influence morphine efficacy.

P-gp is expressed in the capillary endothelium of the blood–brain barrier and acts as an efflux pump, preventing intracellular accumulation of its substrates. Morphine and M6G, methadone and pethidine have been shown to be P-gp substrates.²⁵ P-gp may limit morphine entry into the brain as morphine induced greater analgesia (with greater morphine brain concentration) in knockout mice compared with wild-type.²⁶ However, analgesia was not greater in knockout mice treated with M6G,²⁶ suggesting that P-gp does not modify M6G pharmacodynamics.²⁷ According to Wandel *et al.*²⁸, morphine is a P-gp substrate but with less clinical relevance than other drugs such as loperamide. In patients undergoing colorectal surgery, Coulbault *et al.*²⁹ investigated the influence of genetic factors on adverse events after surgery. The ABCB1 GG-CC diplotype was a borderline-significant predictive factor of morphine adverse events.²⁹ In women undergoing caesarean section, Sia *et al.*³⁰ did not report significant influence of *ABCB1* SNP (notably C3435T) on postoperative intravenous PCA morphine consumption, pain scores and adverse effects within the first 24 h. Conversely, other teams demonstrated a clinical significance

of SNP C3435T in reducing analgesic requirement in patients who were on chronic oral morphine therapy.^{16,30} Lötsch *et al.*³¹ suggested that the main reason for that discrepancy could be the preferential blockade of P-gp at the intestinal level and not at the blood–brain barrier. In our study, analgesic effects of intravenous morphine were not dependent on P-gp expression. However, P-gp polymorphisms (ex-21 and ex-26) were significantly associated with morphine concentration but the prediction of the model was poor as shown by the low value of R^2 (0.04).

A common polymorphism in *COMT*, pVal158Met, leads to a three-fold to four-fold reduction in enzyme activity. This SNP may explain part of the interindividual difference in the adaptation and response to pain and may be involved in morphine dosing requirements and adverse events.³² Kolesnikov *et al.*³³ observed that patients with *OPRM1* and *COMT* G 1947 (Val158Met) genotypes required less morphine in the early postoperative period using PCA. Nausea and sedation scores were also lower during the postoperative period for heterozygous patients.³³ De Gregori *et al.*³⁴ demonstrated an association between morphine consumption during the first 24 h and *COMT* haplotypes; Met/Met homozygous patients required lower morphine doses than other patients. In our

study, the Val158Met polymorphism of the COMT gene was associated with neither changes in morphine consumption nor morphine-related adverse events in the postoperative period.

There are few data regarding the pharmacogenetic contribution to major morphine-related adverse events such as respiratory depression. Romberg *et al.*¹¹ observed that despite a major decrease in analgesic response to M6G, the OPRM1:c118A<G single polymorphism did not protect against respiratory depression, but only 16 healthy volunteers were included and studies with larger samples sizes are probably required.¹¹ In a small sample of 10 healthy volunteers, Oertel *et al.*³⁵ observed that OPRM1 118A>G polymorphism influenced the respiratory depressive effects of alfentanil. Higher (2 to 4 times) alfentanil concentrations were needed in homozygous carriers of the variant 118G allele to produce the same degree of analgesia, and higher (10 to 12 times) alfentanil concentrations were needed to produce the same degree of respiratory depression compared with wild-type subjects.³⁵ In 88 healthy adolescents undergoing spinal fusion for scoliosis, Chidambaran *et al.*³⁶ showed that the risk of respiratory depression was significantly higher (OR 5.6, 95% CI, 1.4 to 37.2) in patients with AA genotype (*OPRM1* A118G polymorphism). The presence of G allele was also associated with higher pain scores.³⁶ In our study, ventilatory depression occurred in 17% of patients in both the PACU and on the ward, and no case of severe ventilatory depression (requiring naloxone) was noted (SPD Table 1, <http://links.lww.com/EJA/A142>). The polymorphism *OPRM1*, *ABCB1* and *COMT* had no significant influence on morphine-related adverse events.

Our study reports negative findings which may be just as important as positive results. It has important strengths: the protocol was registered, the number of genetic polymorphisms investigated was limited and had a theoretical basis, the statistical plan was decided *a priori*, and the statistical analysis performed independently. It should be pointed out that in many domains, initial researches are more likely to be positive and many enthusiastic hypotheses are not confirmed by larger studies with appropriate design and reporting.³⁷ We cannot rule out that a larger study could indicate significant gene polymorphism, but we consider that if a true difference does exist, its magnitude is probably weak and thus not clinically significant. However, three other points deserve discussion, the role of ethnicity, haplotypes and gene–gene relationship.

Ethnic differences in the frequency of the A118G variant and effects on opioid consumption have been noted and very few studies of acute administration of morphine after surgery and A118G SNP in whites have been published.¹⁷ When these genetic effects occur, they are strongest in Asian patients.¹⁸ Ethnicity interacts with the genes in pain sensitivity, opioid requirements and

opioid-related adverse events and may explain the significant effects of various SNP in heterogeneous populations.³⁸ Hastie *et al.*³⁹ compared three groups of healthy young adults, African-Americans, nonwhite Hispanic and non-Hispanic whites, to identify ethnic differences in *OPRM1* allelic association with experimental pain responses. In this study, the G allele was associated with decreased pain sensitivity among whites only.³⁹ In a meta-analysis (18 studies, 4607 patients), Hwang *et al.*¹⁸ observed that the *OPRM1* A118G polymorphism was associated with the requirement for postoperative opioids in Asians but not in whites. The low frequency of polymorphism in whites may also affect results and does not allow the demonstration of any consequence of genetic variation of morphine requirement and morphine-related adverse events.¹⁸

Lastly, the gene–gene approach may be interesting in understanding the morphine response or morphine-related adverse events. Kolesnikov *et al.*³³ investigated whether combined *COMT* and *OPRM1* contributed to the morphine response in the postoperative period. The heterogeneous patients with *OPRM1* A118G and *COMT* G1947A mutation consumed less morphine in the PACU and 48 h after surgery in comparison with homozygous patients of the 118 variant.³³

There is no clear and reproducible evidence of a pharmacogenetic contribution to pain response to opioids, and it is probably premature to integrate pharmacogenetics into the clinic with respect to pain control, at least in the postoperative period.^{18,24} The lack of influence of genetics on morphine requirement, pain score and morphine-related adverse events, may be due to greater impact from environmental factors, patient medical history and the influence of other gene polymorphisms than those studied.⁴⁰

The following limitations should be considered when assessing the clinical relevance of our results. First, we only used morphine, and pharmacodynamic and pharmacokinetic properties of other opioids used in the perioperative period may differ. However, to date, there is no study demonstrating that the genetic polymorphisms we studied may have had a markedly different effect according to the opioids used. Second, morphine-related adverse effects were not severe and, because of their rare occurrence, the power of our study precludes any conclusion regarding the association of genetic polymorphisms and the most severe morphine-related adverse events such as severe respiratory depression. Lastly, our study was not designed to perform genome-wide investigations, and we cannot exclude that SNP at other loci could make a significant contribution to morphine pharmacokinetics or dynamics.

In conclusion, in whites undergoing major orthopaedic surgery, we failed to identify clinically relevant data that could indicate that genetic polymorphisms of

OPRM1, *ABCB1* and *COMT* might significantly influence morphine efficacy and safety.

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