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Modelling the PKPD of oxycodone in experimental pain — Impact of opioid receptor polymorphisms

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ABSTRACT

Background: Polymorphisms in the opioid receptor genes may affect the pharmacodynamics (PD) of oxycodone and be part of the reason behind the diversity in clinical response. The aim of the analysis was to model the exposure–response profile of oxycodone for three different pain variables and search for genetic covariates. Model simulations were used to predict how population and effect-size impact the power to detect clinical significant SNPs.

Method: The population pharmacokinetic–pharmacodynamic (PKPD) model of oral single-dosed oxycodone was based on pooled data from three published studies in healthy volunteers. Pain tolerance data from muscle pressure (n = 36), visceral pressure (n = 54) and skin pinch (n = 34) were included. Genetic associations with 18 opioid-receptor SNPs were explored using a stepwise covariate approach. Model simulations were performed using the estimated model parameters.

Results: None of the selected SNPs were associated with analgesic response of oxycodone at $P < 0.001$. Baseline response in muscle cuff pressure was associated with OPRK1 rs7016778 and rs7824175 ($P < 0.001$). Simulations indicated that large differences in drug response between genotypes (>50% for similar population sizes) or large populations (n > 200 for a 20% response difference) are necessary to identify clinical significant SNP effects due to high population variability.

Conclusion: A population PKPD model has been developed for oral oxycodone using three different pain variables to explore impact of genetic covariates and study design. None of the selected polymorphisms were significantly associated with analgesic response of oxycodone, but an association of baseline response in muscle cuff pressure with two OPRK1 SNPs was identified.

1. Introduction

Many patients treated with opioids have inadequate pain relief, partly explained by the large inter-individual variability in analgesic response (Breivik et al., 2008; Varrassi et al., 2010).

Oxycodone is extensively used in the clinic for the treatment of moderate–severe pain (Lalovic et al., 2006). Compared to morphine little is known about the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of oxycodone and the conclusions from the few population PKPD studies published are hampered by limited population sizes often in the range 4–12 subjects (Lalovic et al., 2006; Leow et al., 1992; Lugo and Kern, 2004; Mandema et al., 1996). Variation in the PK characteristics of oxycodone may be part of the reason behind the diversity in clinical response to oxycodone (Pan et al., 2007). However, factors that impact PD may also be part of the explanation for the variability in analgesic response (Nielsen et al., 2014). Single-nucleotide-polymorphisms (SNPs) in the μ-, δ- and κ-opioid receptor genes (OPRM1, OPRD1, OPRK1) encoding for the opioid receptors have gained increasing prominence as an explanation of some of this variability (Lotsch et al., 2013).

However, so far results of genetic association studies have been inconsistent, and experimental findings have been difficult to demonstrate in clinical settings and replication studies (Holliday et al., 2013; Kim et al., 2006; Klepstad et al., 2011; Lotsch and Geisslinger, 2006; Walter and Lotsch, 2009; Zwisler et al., 2011). In addition, most previous studies have only investigated the A118G variant of the OPRM1

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Table 1
Overview of study demographics and included pain stimulations.

PK analysis	Study 1 [19]	Study 2 [20]	Study 3[a] [21]
N	19	15	21[b]
Sex % F:M	58:42	0:100	52:48
Age (years)	30,9 (22–45)	25,3 (19–34)	27.7 (20–48)
BMI (kg m^{-2})	23,15 (18.3–30.5)	23,7 (20.5–27.4)	22.9 (20–26)
PD analysis	Pain method		
Skin pinch (kPa) (n = 34)	+	+	−
Muscle pressure (kPa) (n = 36)	−	+	+
Visceral pressure (mL) (n = 54)	+	+	+[c]

[a] Subjects were exposed to hyperalgesia pre-dose by administration of acid/capsaicin.
[b] One subject was excluded in the PK analysis due to all data missing.
[c] One subject was not included in the visceral pressure analysis due to no data.

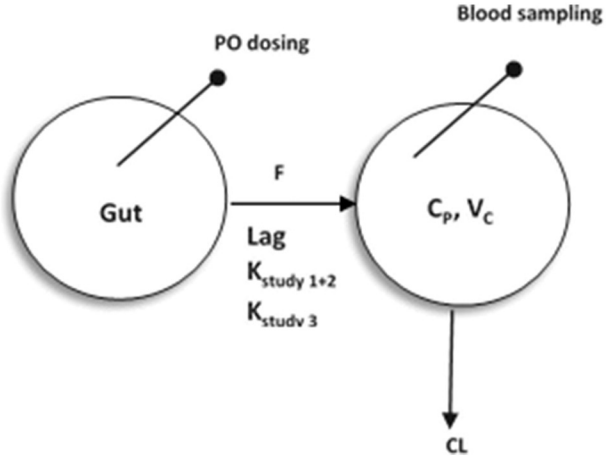

Fig. 1. Final PK compartment model. F: Bioavailability, Lag: lagtime, PO: per-oral, CL: Clearance, K absorption rate constant for study 1 + 2 and study 3, Cp: Plasma concentration, Vc: volume of distribution.

gene (Nielsen et al., 2014). Recently it has been suggested that the resulting pain phenotype is dependent on the contribution of multiple genetic factors, each with individual small effects. This interplay may result in polygenic determinants that involve numerous SNP combinations (Lotsch, 2011). A quantitative understanding of how multiple SNPs across the opioid receptor genes affect analgesic response of oxycodone is therefore warranted. Non-linear mixed effects (also referred to as 'population') modelling is a strong tool to identify and describe relationships between a subject's characteristics and observed drug exposure and response. Population modelling allows simultaneous evaluation of all individuals in a population. This approach makes it possible to estimate population mean parameters (CL, V etc.) while simultaneously quantifying inter- and intra-individual variability and the influence of individual explanatory factors (covariates) including SNPs (Mould and Upton, 2012). By using experimental pain in healthy volunteers possible confounders in subjective pain perception that could arise in the clinic are reduced and the investigator has full control over the induced pain (Reddy et al., 2012). The hypothesis was that analysis of selected opioid SNP variants explains part of the variability associated with clinical response to oxycodone analgesia.

The aim of the present analysis was to model the time-exposure–response profile of oxycodone for three different pain variables and search for genetic associations with analgesic response. The model was used to predict how population size and effect size impact the power to detect clinically significant SNP effects.

2. Materials and methods

2.1. Study design

Data were collected from three previously published randomized, double-blind experimental pain studies in healthy volunteers (Staahl et al., 2006; Arendt-Nielsen et al., 2009; Olesen et al., 2010a). These studies will be referred to as study 1, 2 and 3 respectively. All three studies were conducted in accordance with the Declaration of Helsinki and approved by the local ethical committee. Informed consent was obtained from all subjects before any study related procedures were performed. A previous paper that included the same data and polymorphisms using conventional paired t-testing, not accounting for PKPD relationships and multiple testing has been published recently (Olesen et al., 2015). Population PKPD models of the individual study 2 and 3, not searching for genetic covariates have been published previously (Olesen et al., 2010b, 2013).

Briefly, the experimental design of the investigations was as follows. A total of 55 healthy opioid-naïve volunteers were included in the study. 4 subjects participated in two of the included trials. Subjects were administered a single dose of oxycodone as a 15 mg oral solution and placebo with identical appearances at two different occasions at least one

Table 2
Overview of SNP distribution in the population. 50 subjects were genotyped as 4 subjects participated in two trials. AA is the percentile homozygous for the A allele, AB is the percentile heterozygous for the A and B alleles and BB is the percentile homozygous for the B allele.

Gene	SNP #	RS code	Variation (A/B)	% — wildtype (AA)	% — heterozygous (AB)	% — homozygous (BB)
OPRK1	1	16918875	C/T	96	4	0
OPRK1	2	6473799	T/C	9	40	51
OPRK1	3	1365098	G/T	40	47	13
OPRK1	4	963549	G/A	7	25	67
OPRK1	5	10504151	T/C	82	18	0
OPRK1	6	7836120	A/G	58	38	4
OPRK1	7	7016778	T/A	69	31	0
OPRK1	8	7824175	G/C	5	16	78
OPRD1	9	1042114	G/T	80	20	0
OPRD1	10	2234917	C/T	18	47	35
OPRD1	11	533123	G/A	71	25	4
OPRD1	12	419335	A/G	55	29	16
OPRD1	13	2236857	T/C	35	22	44
OPRM1	14	621029	G/T	98	2	0
OPRM1	15	1799971	A/G	80	18	2
OPRM1	16	563649	C/T	84	16	0
OPRM1	17	9479757	G/A	78	20	2
OPRM1	18	533586	C/T	13	45	42