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1. Introduction

Oxycodone (Oxy) is N-demethylated (CYP3A) into noroxycodone (Nor) and O-demethylated (CYP2D6) into the more active opioid moieties oxymorphone (Omo) and noroxymorphone (Nomo), which might account for the analgesic effects of oxycodone. The aim of the study was to evaluate the relative contribution of CYP2D6 and CYP3A activities to the PD and PK of Oxy in previously genotyped volunteers for CYP2D6.

2. Methods

2.1. Design: 5-arm crossover randomized, double-blind, placebo-controlled, PK-PD study in 10 healthy genotyped males (2PM, 6EM, 2UM for CYP2D6, AmpliChip™) randomly assigned to receive on 5 occasions, 2-weeks apart:

- ✓ Oxy (0,2 mg/kg) 2h after 400 mg ketoconazole (Keto) and 100 mg quinidine (Quin).
- ✓ Oxy 2h after Keto and placebo (P).
- ✓ Oxy 2h after Quin and P.
- ✓ Oxy 2h after P and P.
- ✓ P 2h after P and P.

Naloxone (NX) iv was given 1.75 h after Oxy at each session.

2.2.1. Phenotyping: CYP2D6 and CYP3A4 activities (phenotype) were assessed with oral microdoses of 2.5 mg dextromethorphan (8h urine collection) and 75 µg midazolam (blood sample taken after 30 min)

2.2. Pharmacodynamic assessment:

- Objective pain threshold:** detection of a polysynaptic nociceptive flexion reflex (NFR) in response to electrical stimulations (Viking IV Nicolet, Madison) applied transcutaneously (sural nerve) recorded by electromyography on the ipsilateral biceps femoris.
- Subjective pain threshold (SPT) in response to electrical stimulation:** estimated by numerical rating scale, sensitive category scale, and affective category scale.
- Cold and hot thermal perception and pain thresholds:** assessed by a thermode (Nicolet sensation WinTSA II) operating on the Peltier principle.
- Pain tolerance threshold:** assessed by the cold pressor test (immersion of the left hand into child water).
- Psychomotor performance:** measured by the digit symbol substitution test (DSST).
- Pupil size:** by a digital pupillometer (NeuroOptics PLR-100, Pupillometer, California)
- Side effects** spontaneously reported collected (number and severity).
- Sedation, oxygen saturation and vital signs.**

2.3. Pharmacokinetic assessment

Plasma concentrations of oxycodone and metabolites (noroxycodone Nor, oxymorphone Omo, noroxymorphone Nomo) were assessed by a validated assay using a CS-LC-MS/MS. The LLOQ was 100pg/ml for Oxy and Omo, and 50pg/mL for Nor and Nomo.

2.4. Data collection: The whole session lasted 8h. PD data were collected before (t=0) and up to 6h (at t = ½, 1, 1.5, 2, 3, 6 h) after drug administration. Blood samples were obtained at predetermined time points in EDTA-containing tubes (0, 0.5, 1, 1.5, 2, 3, 6, 24h).

3. Results

Pharmacodynamics

Drug inhibitions:

Quinidine (Quin) reduced oxycodone (Oxy) analgesic efficacy whereas ketoconazole (Keto) did the opposite. No difference between placebo and Oxy was demonstrated in the NFR and SPT after electrical stimulation. After Quin the peak pain threshold after electrical stimulation was 30% lower than Oxy alone (p=0.019) and pupil effects were less pronounced (Emin: 4.54 vs 4.43 mm, p=0.00325) [Fig. 1, 2 and 3]. Inversely, Keto enhanced the magnitude of Oxy PD effects (20-70% higher than placebo). As compared to Oxy alone, Keto increased the NFR AUEC90 by 15% (p=0.037) and increased pupil effects by 20% (3.6 vs 4.43 mm, p=0.02) [Fig. 2 and 3].

CYP2D6 polymorphism:

CYP2D6 activity was inversely correlated with the SPT (ps = -0.636, p=0.048) and pain tolerance (ps = -0.64, p=0.046). After Oxy alone, SPT AUEC90 was 6-times higher in UM than EM (p= 0.052). Inversely Emax was 2.6-times lower in PM-IM than UM (p=0.052) [Fig 2]. All volunteers except the PM had pupillary constriction after Oxy, stronger in UM [Fig 3b].

Adverse events and naloxone:

60 adverse events (all mu-opioid related) were reported in 23/50 sessions. CYP3A blockade dramatically increased the risk of ADRs particularly in CYP2D6 UM. Naloxone reversed oxycodone PD effects. Withdrawal symptoms were observed in UM and EM within minutes after naloxone injection.

Fig 5. AUC1460 depending after each treatment in various CYP2D6 genotypic group

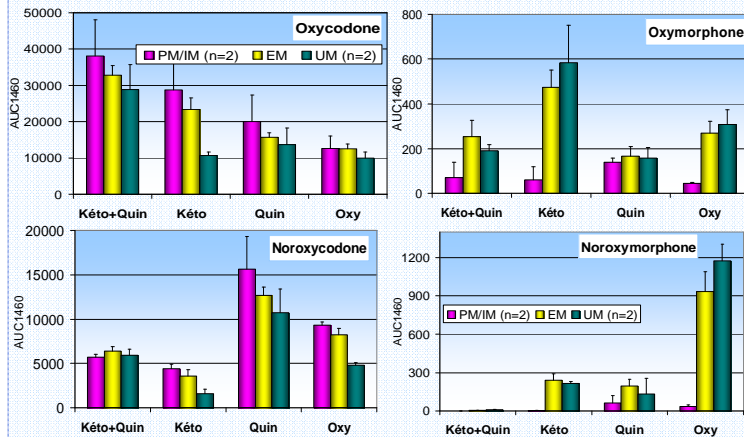


Fig 1. Subjective pain threshold over 6h after each treatment

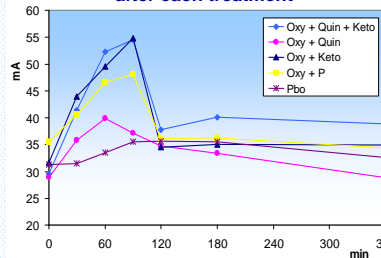


Fig 2. Subjective pain Emax after each treatment in CYP2D6 genotypic groups

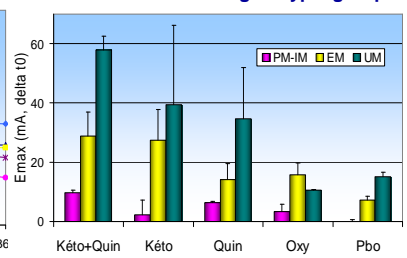


Fig 3. Pupil size over 6h (3b insert: after Oxy alone in CYP2D6 genotypic groups)

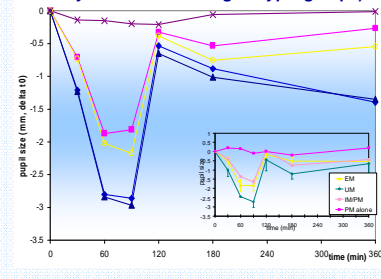
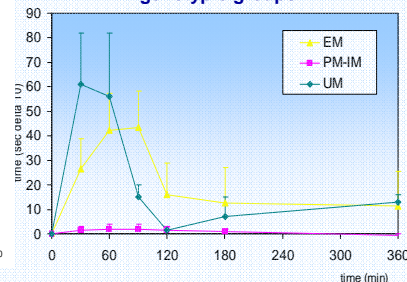


Fig 4. Cold pressor over 6h in CYP2D6 genotypic groups



Pharmacokinetics

Drug inhibitions: Blocking CYP2D6 with Quin reduced Omo and Nomo Cmax by 40% (p=0.01) and 80% (p=0.0009), whereas Keto reduced Nor and Nomo exposure by 80% (p=10-7 and 0.0005). Nor AUC∞ rose by 70% (p=0.0004) after Quin and Omo AUC∞ was 3.5 times higher (p=0.0004) after Keto. Quin+Keto had a cumulative effect on Oxy's PK (AUC∞ x3, p=2.10-10) [Fig 5].

CYP2D6 polymorphism: CYP2D6 activity was strongly correlated with Omo and Nomo PK (-0.71 < ps < -0.92, p < 0.05). Omo Cmax was 62% and 75% lower in PM than EM and UM (p=0.015 and 0.007). Nomo Cmax reduction was even more pronounced (90%, p=0.003). Nor AUC∞ was 43% and 50% lower in UM than EM and PM (p=0.032 and 0.012).

PK-PD correlations

Omo and Nomo Cmax were correlated with the NFR (ps = 0.673 and 0.111, p < 0.05) and SPT (ps = 0.709 and 0.661, p < 0.05) AUEC90 after electrical stimulation. Omo AUEC90 was the only independent predictor of the SPT AUEC90 after electrical stimulation in a multivariable analysis (linear mixed effect model)

4. Conclusions

- ✓ Modulations of CYP3A and 2D6 activities have a dramatic impact on the analgesic efficacy, safety and pharmacokinetics of oxycodone, which is significantly influenced by CYP2D6 genetic polymorphism.
- ✓ Oxymorphone appears to be the active metabolite mainly responsible for oxycodone analgesic efficacy.
- ✓ The PD effects of oxycodone are principally mediated by the µ opioid receptor reversed by naloxone.