Pharmacogenetics of methadone adverse events

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Introduction

Opiates, opioids, and prescription opioids continue to be one of the main problematic drug groups worldwide. The main treatment strategy in opioid use disorder is opioid agonist maintenance which objective is to stabilize brain neurochemistry by replacing a short-term acting opioid with a long-term acting one. Opioid agonist maintenance treatment is designed to minimize the effect of the euphoria associated with the administration of illicit opioids, and eliminates opioid withdrawal syndrome.[1] The two main opioids for maintenance treatment are methadone and buprenorphine. Methadone is the most prescribed treatment, with clear data on efficacy.1 Adverse events of methadone are, in general, mild and tolerable: constipation, sweating, and insomnia; however, there are two major adverse events related to methadone: the risk of respiratory depression and ventricular arrhythmia.[2] The occurrence of adverse events involve from the reduction of compliance to health threatening incidents. The risk for mild and severe adverse events may be related to patient's genetic background.

Aims

To analyze the influence of genetics on the occurrence of adverse events in methadone maintenance treatment.

Material and methods

Systematic review of the literature regarding the influence of genetic variability in the appearance of adverse events in methadone maintenance treatment.

Results

Evidence was found for genes coding for opioid receptors (*OPRM1*, *OPRK1* and *OPRD1*) related with sleep disturbances, withdrawal symptoms and libido changes. Genes coding for Cytochrome P450 enzymes, mainly CYP3A4 and CYP2B6, showed an association with withdrawal syndrome symptoms and sedation. Interestingly, poor metabolizer profile at CYP2B6 was associated to longer QTc intervals than extensive metabolizers, increasing the risk of severe arrhythmia and death. Cardiac adverse events have been related to the (*S*)-enantiomer and not to (*R*)-enantiomer. Main characteristics of the reviewed studies are summarized in Table 1.

Conclusions

The implementation of regular electrocardiogram monitoring in patients receiving methadone treatment is mandatory. Alternative to (*R,S*)- methadone in these cases must be provided (i.e. levo-methadone; morphine sustained-release...). Although promising results, majority of the studies did not perform a confirmation evaluation, and some sample sizes are small, being difficult to establish clear recommendations.

References

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Table 1. Main studies assessing genetic variability and its influence in adverse events in methadone maintenance treatment (MMT).

Study	Sample characteristics	Gene (SNPs)	Results
		Minor adverse events	
Chen et al., 2011	366 Han Chinese MMT patients	*CYP3A4* (rs4646440 and rs224248)	The SNPs were associated with the severity of withdrawal symptoms and methadone adverse effects.
Tian et al., 2012	366 MMT patients in Taiwan	*UGT2B7* rs6600879 rs6600880 rs4554144 rs11940316 rs7438135 rs7662029 rs7668258 rs7439366 rs4292394 rs6600893	Significant associations with severity of withdrawal symptoms, pupil size and tremor.
Wang et al., 2012	366 Han Chinese MMT patients	*OPRM1* rs1074287 rs6912029 rs1799971 rs12209447 rs510769 rs3798676 rs553202 rs499796 rs7748401 rs495491 rs10457090 rs589046 rs3778152 rs563649 rs2075572	Changes in libido scores (dominant model) and insomnia scores (recessive model) were associated with rs1074287; rs6912029; rs12209447; rs510769; rs3798676; rs7748401; rs495491; rs10457090; rs589046; rs3778152; rs563649; rs2075572, after adjusting for age, gender and BMI.
Wang et al., 2014	366 Taiwanese MMT patients	*OPRK1* 17 SNPs	Six SNPs from rs7843965 to rs1051660 (intron 2 to exon 2) were significantly associated with body weight. A haplotype of 4 SNPs rs7832417-rs16918853-rs702764-rs7817710 (exon 4 to intron 3) was associated with bone or joint aches and with the amount of alcohol use. The haplotype rs10958350-rs7016778-rs12675595 was associated with gooseflesh skin, yawning and restlessness withdrawal symptoms.
Wachman et al., 2015	86 newborns and their mothers (98% white, non-Hispanic)	80 SNPs in 14 candidate genes: *OPRM1* *OPRD1* *OPRK1* *PENK* *POMC* *PDYN* *PNOC* *OPRL1* *COMT* *GAL* *BDNF* *SLC6A2* *SLC6A3* *SLC6A4*	Carriers of the G allele at *OPRM1* (rs1799971) were at lower risk of experience neonatal withdrawal syndrome due to MMT in their mothers.
Zahari et al., 2016	165 Malay males in MMT	*OPRM1* rs1799971 rs2075572	The AC/AG diplotype for the A118G and IVS2 + G691C polymorphisms is associated with better sleep quality.
Zahari et al., 2016	148 Malay male MMT patients	*CYP2B6* (*6 allele) rs3745274	The *CYP2B6**6 allele was associated with a lower pain threshold and lower pain tolerance.
Sharafshah, et al., 2017	202 Iranian patients in MMT	*OPRD1* rs2236855	T allele associated with reduced libido.
Albonaim et al., 2017	202 Iranian patients in MMT	*OPRK1* (rs997917 and rs6985606)	C allele associated with insomnia. T allele associated with co-incidence of insomnia and change in libido.
		Serious adverse events	
Wong et al., 2003	21 Methadone related deaths	*CYP 2D6 alleles* rs35742686 (*CYP2D6* *3), rs3892097 (*CYP2D6* *4), whole gene deletion (*CYP2D6* *5)	The prevalence of poor metabolizer was higher but not significantly different from that of a control group.
Eap et al., 2007	179 Caucasian MMT patients Methadone dose: 145±83 mg/day	*CYP2B6* (*6) rs3745274	The mean QTc was higher in *CYP2B6* slow metabolizers (439 ± 25 ms) than in extensive metabolizers (421 ± 25 ms; P = 0.017)
Bunten et al., 2010; 2011	40 individuals with deaths associated with MMT	*CYP2B6**6 (rs3745274) *OPRM1* (rs1799971)	*CYP2B6*: in the group of slow metabolizers, the postmortem plasma concentrations of methadone were higher compared to other genotypes. *OPRM1*: Carriers of the 118GA genotype presented higher benzodiazepine plasma concentrations in the methadone related deaths, but not in the morphine related deaths
Wang et al., 2013	366 MMT patients in Taiwan	*CYP2C19* rs4986893 rs4244285	Methadone daily doses of both the extensive metabolizers (58.78 ± 32.69 mg/d, p = 0.004) and intermediate metabolizers (57.64 ± 28.69 mg/d, p = 0.001) were significantly higher than that of the poor metabolizers (40.45 ± 22.17 mg/d) Poor metabolizers had higher plasma concentrations of both dose-corrected plasma concentrations of (*R*)-methadone (p = 0.002) and (*R*)-EDDP (p = 0.03) than extensive metabolizers.
Richards-Waugh et al., 2014	136 methadone accidental overdoses: 133 involved methadone-only overdoses 95 combined methadone/ benzodiazepine overdoses	*CYP3A4* rs2246709 rs3735451 rs4646437 rs2242480 rs4987161 rs4986910 rs2740574	Two SNPs: rs2242480 and rs2740574 demonstrated an apparent enrichment within the methadone-only overdose fatalities compared with the control group and the general population.
Icick et al., 2014	108 Caucasian stable MMT patients	*OPRM1* rs1799971	The A118G polymorphism was not associated with lifetime suicide attempts. Suicide risk was associated with major depression diagnosis.
Hajj et al., 2014	82 stable methadone patients Methadone dose: 57 (range: 10–320)	*KCNH2*: rs1805123 *KCNE1*: rs1805127 *KCNE1*: rs2236609	Each copy of a Lys allele at codon 897 of *KCNH2*, the gene that encodes the cardiac potassium voltage-gated channel hERG, was associated with a15.4 ms longer Qtc.
Carlquist et al., 2015	25 MMT patients: Caucasian (74 %) Hispanic (19 %) African American (3 %) Native American (3 %)	*CYP2C19*	Carriers of the *CYP2C19*2* variant presented higher concentrations of plasma EDDP, (*S*)-EDDP, and (*R*)-EDDP (p=0.004). The methadone dose and the plasma EDDP concentration corrected for dose were both significantly associated with QTc.
Ahmad et al., 2017	125 Caucasian methadone fatalities	*CYP2B6* rs2279344 rs3211371 rs3745274 rs4803419 rs8192709 rs8192719 rs12721655 rs35979566	The frequencies of SNPs rs3745274 (*9), and rs8192719 (C21563T) were enhanced in the methadone-only group. Higher blood methadone concentrations were observed in individuals who were genotyped homozygous for SNP rs3211371 (*5) (1.67 ± 0.85) as compared to either the heterozygote (0.52 ± 0.08) or homozygous ancestral genotype (0.59 ± 0.05), p<0.05.