THE ROLE OF CYP3A5 IN METHADONE METHABOLISM: A CASE REPORT

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Maintenance treatment with methadone often represents first line therapy for heroin addiction, contributing, by stopping or reducing heroin use, to a drop in mortality. The high oral bioavailability of methadone, its long elimination time requiring a single daily dose, and the availability of a specific antagonist support its use in the chronic relapse disorder.
We report a case of methadone maintenance therapy failure in an opiates addict patient aged 25. Methadone was first used at the dose of 20 mg/daily; since Abuscreen Urinary test resulted negative, pharmacological interactions affecting drug disposition and poor compliance were first investigated, and then both ruled out. Moreover, in order to prevent withdrawal symptoms physicians decided for a dose augmentation to 60 mg/daily. Abuscreen Urinary test again resulted negative, while blood chemical tests revealed a significant decrease in methadone plasma levels (200 ng/mL) with an increase of EDDP (51.5 ng/mL), the main methadone metabolite. The pharmacokinetic of methadone varies greatly among individuals and an increased metabolism, causing lower blood level of the drug, may determine therapy failure. Several cytocromes are involved in methadone metabolism: such as CYP3A4, which provides drug N-demethylation, and CYP2D6. The genotypization of cytochrome P450 metabolic pathways and P-glycoprotein gene showed that our patient did not carry any CYP3A4 or CYP2D6 detrimental allele and that he was heterozygous for the CYP3A5*3 allele and for two SNPs in the P-glycoprotein gene (1236C/T and 3435C/T). These findings suggested a putative differential role for CYP3A5 and P-gp in methadone metabolism and disposition.