Genetics and variability in opioid pharmacology

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In pain management it is apparent that patients' respond differently to opioid therapy and current evidence suggests that this is related to genetic variability. Genetics can affect both pharmacokinetics and dynamics. Genetic variability in non-opioid systems may also indirectly influence clinical opioid efficacy e.g. genetic inactivity of cytochrome P450 (CYP) 2D6 occurs in about 8% of the Caucasian population (only 1-2% of Chinese) and renders codeine ineffective (lack of morphine formation), decreases the efficacy of tramadol (lack of formation of the active O-desmethyl-tramadol) and slightly decreases the clearance of methadone. Another 5% have multiple copies of the CYP2D6 gene and are ultrarapid metabolisers. Opioid bioavailability can be altered by the function of membrane transporters e.g. P-glycoprotein, thereby affecting CNS distribution and elimination and even drug uptake into metabolising organs/cells. Polymorphisms in enzyme systems also affect the formation of active metabolites e.g. M-6-G, or opioid clearance. Variability in an enzyme-degrading catecholamine (COMT) gene may alter the efficacy of morphine

Receptor binding and a wide range of pharmacological studies have proposed several μ receptor subtypes, but only one μ opioid receptor (Oprm) gene has been isolated. These variants all show the same selectivity for μ opioids but major differences in binding affinity, potency and efficacy among these variants as well as in their anatomical localization. These variants may provide insights into the wide range of opioid responses among these agents observed clinically and opens new avenues in designing selective drugs based upon their efficacy and potency rather simple binding affinity. Pharmacogenetics may be able to individualize pharmacotherapy and improve care by predicting the optimal dose and avoiding side effects and toxicity in individual patients.

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References

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