The COMT Val158Met polymorphism modulates in an opposite-direction the clinical response to intrathecal morphine and triptans

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Catechol-O-Methyltransferase (COMT) is an enzyme which catalyzes the metabolic O-methylation of catecholamines, such as dopamine, epinephrine, and norepinephrine. Variations in COMT catabolism result in abnormal synaptic dopamine levels, ultimately impacting on dopaminergic stimulation of the post-synaptic neuron. The common variation Val158Met of the COMT gene causes a substitution from a valine to a methionine at position 158 leading to a three-to four-fold reduced catabolism of dopamine and a higher neurotransmitter availability (Lotta et al, 1995). As it is well known from literature, altered dopamine levels are involved in pain processing, suggesting a role of COMT genetic variations in the interindividual variability in human pain phenotypes and response to analgesics. The Val158Met variant has been shown to influence efficacy of morphine used for cancer pain, for which the Met/Met genotype group needs lower morphine doses than Val/Val genotype group (Rakvag et al, 2005). However, some other reports in cancer patients were unable to demonstrate an involvement of Val158Met on the opioid dose requirement (Klepstad et al 2011). Furthermore, dopaminergic system hypersensitivity has been suggested as a pathophysiological mechanism of migraine on the basis of the pharmacological efficacy of dopamine antagonists in acute migraine treatment. The COMT Val158Met variant is involved in phenotypic expression of migraine without aura (MwoA), with 158 Met-allele carriers experiencing a higher pain intensity of headache compared to wild type patients (Park et al, 2007). Hence, it is plausible that interindividual variability in COMT activity may modulate the response to medications effective in headache pain management, including triptans. The aims of this study were a) to confirm the association between COMT Val158Met and the analgesic response to intrathecal morphine in patients affected by chronic musculoskeletal low back pain; b) to assess for the first time the relationship between Val158Met polymorphism and triptan response in two independent cohorts of migraine patients. The logistic stepwise regression analysis in patients with chronic musculoskeletal low back pain showed that age (OR: 0.90, 95% CI: 0.85-0.96, P=0.002) and the presence of the COMT Met allele (Met carriers vs Val/Val, OR: 0.21, 95% CI: 0.04-0.98, P=0.048) were predictive factors for lower risk of poor analgesic response to intrathecal morphine. Intriguingly, the COMT Val158Met variant in migraine patients influenced headache response to triptans in the opposite direction. Indeed, in a exploratory cohort of MwoA patients in treatment with frovatriptan (n=75), the Met/Met group was found at increased risk to be poor responder to frovatriptan when compared to Val/Val patients (OR: 5.20, 95% CI: 1.25-21.57, P=0.023). According to this, in the validation cohort of migraneurs in treatment with triptans other then frovatriptan (n=123), the logistic stepwise regression analysis showed that COMT Met/Met genotype (vs Val/Val, OR: 4.29, 95% CI: 1.10-16.71, P=0.036) and prophylactic medications (OR: 0.43, 95% CI: 0.19-0.99, P=0.048) were independent risk factors for poor response to triptans. These results underline an opposite role of COMT genotype in modulating the clinical response to two different classes of drugs practiced in pain management, highlighting a complex relationship between cathecolaminergic neurotransmission, pain states and specific analgesic drugs.

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