PHARMACOGENOMICS AND TRIPTANS: A PILOT STUDY OF ASSOCIATION BETWEEN CLINICAL RESPONSE TO RIZATRIPTAN AND SOME CANDIDATE GENES

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Migraine is the most common neurological disorder and affects 6% of males and 15-17% of females. The pathophysiology of this primary headache is still unknown but both neural and vascular mechanisms are known to be involved. One important hypothesis, based on experimental evidence, is that an altered monoaminergic neurotransmission is implicated, particularly of the serotonergic and dopaminergic systems.
Migraine is a complex genetic disease, wherein susceptibility genes and environmental factors both contribute to its development. Migraine attacks are usually treated with triptans, 5-HT_{1B} and 5-HT_{1D} receptor agonists. These receptors are able to cause constriction of intracranial blood vessels, to modulate neurotransmitter release from neuronal terminals and to block the release of proinflammatory neuropeptides. Up to 15% of migraineurs fail to respond to triptans. Genetic factors may contribute to this interpatient difference. Rizatriptan is a 5-HT_{1B} receptor agonist, which has proved to be considerably efficient in treating migraine attacks. Genetic differences in the clinical response to rizatriptan could be explained by various genes: the HTR1B, encoding the 5-HT_1 receptor subtype, representing the pharmacological target of the drug; the MAO-A gene, encoding the monoamino-oxidase, the SLC6A4 gene, encoding the serotonin transporter, and the DRD2 gene, encoding the D_2 receptor, these latter two being involved in the pathogenesis of migraine.
Fifty unrelated patients affected by migraine without aura (IHS) were included. Patients were divided into two groups (responders and non responders) according to clinical response. Gene polymorphisms were assessed by polymerase chain reaction (PCR).
Thirty-one out of fifty patients responded to rizatriptan. Allele and genotype frequencies of SLC6A4, 5-HT1D_{β}, MAO-A and DRD2/BstNI polymorphisms did not differ significantly. A significant difference among the two groups was observed in both allele (p=0.02) and genotype distribution (p=0.03) of DRD2/NcoI.
The significant association with the DRD2/NcoI polymorphism in responders suggests that the DRD2/NcoI C allele is neither necessary, nor sufficient, to determine a positive response to rizatriptan, but it may be considered as a susceptibility factor heralding a good response to rizatriptan. In conclusion, in spite of the small size of the sample examined and the need of replication in other types of population, this study underlines the possible usefulness of a pharmacogenetic strategy as a tool to study potential drug targets.