Migraine and its chronicization to medication overuse headache: a pharmacoepidemiologic pharmacogenetic approach

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Introduction: Medication overuse headache (MOH) is a chronic secondary daily headache induced by the overuse of acute headache medication, including triptans, single and combination analgesics, barbiturates, opioids and ergot alkaloids.[1] Its best available treatment is based on withdrawal from overused symptomatic medications, treatment of withdrawal headache and migraine prophylactic therapy.[2] Unfortunately, about 30-45% of patients with MOH do not improve after withdrawal therapy and relapse in symptomatic drug overuse within 1 year.[3] Many efforts are currently ongoing to identify risk factors for migraine chronicization and predictors of MOH prognosis. In this context, we hypothesized that use of pharmacoepidemiologic and pharmacogenetic approaches could improve MOH knowledge, in terms of disease population prevalence and of risk factors. Triptans, which are exclusively indicated for migraine treatment, are fully reimbursed by the Italian NHS. So, in principle, it is possible to identify individual patients' drug intake to estimate the prevalence of triptan use/overuse in an Italian population. In the present study, we aimed to describe the incidence of MOH and the risk of relapse into MOH after 2 months of triptan non-use (withdrawal period) in the Umbria region population by means of 14-year drug prescription data recorded in the period from 1 Jan 2000 to 31 Dec 2013. In addition, in collaboration with C. Mondino National Neurological Institute (Pavia), we conducted a genetic association study to assess the role of rs3781719 (T > C) in the calcitonin gene-related polypeptide-alpha (CALCA) gene and of rs3754701 (T > A) and rs7590387 (C > G) at the receptor activity modifying 1 (RAMP1) locus as risk factors for transformation of episodic migraine into MOH. Calcitonin gene-related peptide (CGRP) is indeed a potent vasodilator agent with an essential role in the pathogenesis in migraine; however, little is known about its function as potential determinant of migraine chronicization to MOH.
Results: About 5.5% of triptan users (N=20861) in Umbria region overused triptans during the observation period. The majority of them (80%) were females, with the mean age of 45 years old. The mean duration of triptan/s overuse was of 5 months, and, intriguingly, males showed a higher triptan consumption compared to females (respectively, median doses: 58 vs 49; P=0.001). The 77% of triptan overusers showed a period of 2 months free from triptan consumption after which the 47% of subjects (N=425; 80% of females) relapsed in acute headache medication with a mean latency period of 9 months. The risk of relapse in triptan overuse is comparable in both sexes (RR 1.04, 95% CI: 0.81-1.34) while it is higher in subject with age comprised between 30 and 49 years. In the pharmacogenetic study, we performed the genotyping on 219 migraine patients and on 130 MOH patients. Carriers of RAMP1 rs7590387GG displayed a lower risk of episodic migraine transformation into MOH (vs C allele carriers, odds ratio [OR]: 0.27, 95% confidence interval [CI]: 0.13-0.57, P = 0.0002). When genotype distribution for RAMP1 rs7590387 was compared between healthy controls (n = 209) and MOH patients, carriers of rs7590387GG were found at lower risk of developing MOH (OR: 0.43, 95%CI: 0.22-0.85, P = 0.011).
Conclusions: Our pharmacoepidemiological description of MOH highlighted that every year, on average, the 2.5% of triptan users had an incident episode of triptan overuse. Moreover, about 50% of triptan overusers relapse in triptan overuse after 2 months of interruption of triptan use. Our findings also show that RAMP1 rs7590387 may have a role in the transformation of episodic migraine into MOH, suggesting a potential impact of genetic variability on MOH susceptibility.

1. Da Silva A. N. and Lake A.E. Headache 2014;54(1):211-7.
2. Tassorelli C. et al. Cephalalgia 2014;34(9):645-655.
3. Katsarava Z. et al. Cephalagia 2005;25:12-15.