

## Factors influencing the disproportional association between triptans and cerebrovascular events within the FDA\_AERS database: causal association or reporting bias?

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Triptans are specific antimigraine drugs. Due to the constriction of the cerebral vessel evoked by triptan intake, in rare cases, these drugs have been associated with the onset of cerebrovascular events (Imitrex<sup>®</sup>). Although epidemiological studies do not suggest an increased risk of stroke (Archambault, 2006), our previous analysis of the FDA Adverse Event reporting System (FDA\_AERS) database found different cerebrovascular events disproportionately reported in association with triptan use. The aim of this study was to identify factors influencing the disproportional association between triptan and cerebrovascular events reported to the FDA\_AERS database. A *case/non-case* analysis was performed (Moore et al., 1997) on adverse events reported to the FDA\_AERS between 2004 and 2010. *Cases* were reports with at least one event assigned to the MedDRA High Level Terms (HLTs) 'Cerebrovascular and spinal necrosis and vascular insufficiency' or 'Cerebrovascular aneurisms and dissection', whereas *non-cases* were all the remaining reports. *Cases* and *non-case* were considered as exposed when at least one triptan was reported as 'suspected' or 'interacting'. Reporting Odds Ratio (ROR) and 95% confidence intervals (95%CI) were calculated on each dataset strata obtained considering potentially confounding/modifying factors: age (<17, 18-44, 45-64, >64), co-reported estrogens/contraceptives (ATC G03AA, G03AB, G03C, G03F) or cardiovascular drugs (ATC C), and 'migraine' (indication of use field). As a sensitivity analysis, subsets containing factors highlighted in the primary analysis were further stratified. On a total of 2,131,688 reports, 7808 concerned triptans. Exposed *cases* were 110 while non-exposed *cases* were 21,409. Triptans-cerebrovascular event combination generated a ROR value of 1,39 (95%CI 1,15–1,68). Among factors considered for the stratification, age between 18 and 45 years (N=53, ROR=4,45; 3,38-5,87) and estrogens/contraceptive use (N=12, 2,99; 1,67-5,34) were striking. In the sensitivity analysis, estrogens/contraceptive use was again associated to a considerable increase of the ROR (N=12, 3,00; 1,68-5,35) within the 'female' stratum. The subset '18-45 years' was further stratified using all the parameters considered: Strong disproportionality signals were obtained for all the strata with ROR ranging from 2,09 (1,24-3,54) within the stratum 'migraine' to 5,75 (3,14-10,55) among males. This study highlighted patient's age of 18-45 years and concomitant use of estrogens/contraceptives as major modifier factors of the disproportional association between triptan and cerebrovascular events within the FDA\_AERS database. Current knowledge on stroke occurrence suggest a particularly increased risk in migraineurs aged less than 45 years and in women treated with oral contraceptives (Larrosa-Campo et al., 2012). In these patients triptan-induced vasoconstriction may potentially add to this risk. Results obtained here identify specific subpopulations to be investigated through large scale analytical studies.

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Archambault ME. (2006) 19: 57-8.

Moore N et al. (1997) *Br J Clin Pharmacol.* 44, 513–18.

Larrosa-Campo D et al. (2012) *Rev Neurol.* 55, 349-58.