Short Communication

Enzyme-Inducing Anti-Seizure Medications Increase Risk of Ischemic Coronary and Cerebrovascular Diseases in the Long-Term

Gaetano Zaccara*

Regional Health Agency of Tuscany, Firenze, Italy

ABSTRACT

Comorbidity between epilepsy and cardiac diseases is frequent. Some Anti-Seizure Medications (ASMs) are associated with an increased risk of cardiac diseases. Enzyme-Inducer ASMs (EI-ASMs) have detrimental effects on some metabolic parameters that promote Atherosclerosis, including homocysteine, serum lipids, C-reactive protein, and uric acid. In a recent study, it has been demonstrated that EI-ASMs are associated with an increased risk of cardiac and cerebrovascular diseases.

Key Words: Anti-seizure medications, Comorbidity, Cardiac diseases, Drug interactions

Correspondence:

Gaetano Zaccara, Regional Health Agency of Tuscany, Firenze, Italy, Tel: 0039 055 2336851; E-mail: gaetanozaccara@yahoo.it

ABOUT THE STUDY

While comorbidity between cerebrovascular diseases and epilepsy has been extensively explored in several studies [1]. More recently it has been observed that in patients with epilepsy there is a higher prevalence of unspecified heart diseases in respect to the general population [2,3]. In addition, structural changes of the heart, mainly characterized by fibrosis and myofibrillar degeneration, have been found at autopsy of patients with chronic epilepsy [4]. Ischemic heart disease, or coronary artery disease, is characterized by narrowed coronary arteries that supply blood to the heart muscle and is caused by a blood clot or by constriction of the blood vessel, usually caused by atherosclerosis.

Up to now, there is not a clear explanation for the finding of this higher incidence of heart disease in patients with epilepsy, although several hypothesis have been proposed. Seizures may have detrimental effects on heart. Repeated surges in catecholamines during Seizures and seizure-induced hypoxemia and myocardial ischemia may cause the observed cardio toxic effects. In patients with severe forms of epilepsy and with this vulnerable myocardial substrate, seizure-related autonomic factors may subsequently trigger life-threatening arrhythmias [5].

Within this scenario, it is important to evaluate the role of Anti-Seizure Medications (ASMs). While a meta-analysis of all placebo-controlled, double-blind studies conducted with ASMs, has demonstrated a lower risk of Sudden Unexplained Death in Patients with Epilepsy (SUDEP) among patients randomized to the active drug than to placebo, treatment with ASMs, when prescribed for reasons different from epilepsy, was associated with an increased risk of Sudden Cardiac Death (SCD) [6,7].

It is important to stress differences but also similarities between SUDEP and SCD. By definition SUDEP is a sudden, unexpected death of someone with epilepsy, who was otherwise healthy and with no other cause of death at autopsy. Each year, more than 1 in 1,000 people with epilepsy die from SUDEP. In such cases there are often signs of a recent seizure close to the time of death and seizure-induced cardiac arrhythmia and breathing disturbances have been advocated as a cause of death [8].

However, in patients with severe epilepsy, there are also non-seizure related arrhythmias that can be life-threatening and may lead to death. SCD is an unexpected death of someone in a stable medical condition with no evidence of a non-cardiac cause and is a consequence of a lethal cardiac arrhythmia. In patients with SCD, heart failure and Ischemic heart disease are detected in the vast majority of cases [9].

It can be speculated that ASMs, for their effects of reducing seizure frequency, have protective effects on heart although these agents are associated with a small absolute increased risk of cardiac death that may be related to their effects on cardiac rhythms. It is known that ASMs affecting sodium channels (Phenytoin, Carbamazepine, Oxcarbazepine, Eslicarbazepine acetate, Lacosamide, Lamotrigine) prolong PR interval and there are also ASMs that may have mild effects of prolonging or shortening QT interval (Phenobarbital, Phenytoin, Carbamazepine, Primidone, Lamotrigine, Zonisamide) [9]. However, arrhythmias caused by ASMs and by seizures are more often observed in subjects with a vulnerable myocardial substrate [5].

Several studies suggest that ASMs that have Enzyme Inducer Properties (EI-ASMs) have detrimental effects on some metabolic parameters that promote Atherosclerosis, including homocysteine, serum lipids, C-reactive protein, and uric acid [10,11] although clinical relevance of these metabolic effects is still controversial. To demonstrate whether EI-ASMs are associated with vascular diseases, pharmaco-epidemiologic studies have been conducted, without univocal results, on large administrative database aimed to assess frequency of occurrence of coronary or ischemic cerebrovascular events in populations of subjects exposed to these drugs in comparison to subjects treated with non EI-ASMs [12-15].

Very recently, a study has been published on a large, population-based cohort of patients with epilepsy that were followed up for more than 319 persons in 10 years (mean follow up of more than 9 years). It has been found that the hazard ratio for incident cardiovascular diseases is significantly higher in patients receiving EI-ASMs and that the association is dose dependent, is more evident in subjects treated with more than one ASM, and increase with duration of exposure reaching clinical significance after 8-10 years from the first prescription of these agents [16].

Cite this article as: Zaccara G. Enzyme-Inducing Anti-Seizure Medications Increase Risk of Ischemic Coronary and Cerebrovascular Diseases in the Long-Term. J Basic Clin Pharma. 2021;12(6):88-89.

CONCLUSION

It can be concluded that EI-ASMs increase the risk of cardiac and cerebrovascular events although this risk increases slowly over a period of several years. Metabolic changes exerted by these drugs are probably the main determinant for these effects although the induction of metabolism with the consequent reduced efficacy of several drugs prescribed for treatment of Atherosclerosis and for cardio end cerebrovascular diseases such as Atorvastatin or Calcium Channel Blockers (CCBs) by EI-ASMs may also have a role.

REFERENCES

1. Gaitatzis A, Carroll K, Majeed A, et al. The epidemiology of the comorbidity of epilepsy in the general population. Epilepsia. 2004; 45(12):1613-1622.
2. Téllez-Zenteno JF, Matijevic S, Wiebe S. Somatic comorbidity of epilepsy in the general population in Canada. Epilepsia. 2005; 46(12):1955-1962.
3. Zaccara G, Lattanzi S, Cincotta M, et al. Drug treatments in patients with cardiac diseases and epilepsy. Acta Neurol Scand. 2020; 142(1):37-49.
4. Dasheiff RM. Sudden unexpected death in epilepsy: A series from an epilepsy surgery program and speculation on the relationship to sudden cardiac death. J Clin Neurophysiol. 1991; 8(2):216-222.
5. Verrier RL, Pang TD, Nearing BD, et al. The epileptic heart: Concept and clinical evidence. Epilepsy Behav. 2020; 105:106946.
6. Ryvlin P, Cucherat M, Rheims S. Risk of sudden unexpected death in epilepsy in patients given adjunctive antiepileptic treatment for refractory seizures: A meta-analysis of placebo-controlled randomised trials. Lancet Neurol. 2011;10(11):961-968.
7. Bardai A, Lamberts RJ, Blom MT, et al. Epilepsy is a risk factor for sudden cardiac arrest in the general population. PLoS One. 2012; 7(8):e42749.
8. Devinsky O. Sudden, unexpected death in epilepsy. N Engl J Med. 2011;365:1801-1811.
9. Zaccara G, Lattanzi S. Comorbidity between epilepsy and cardiac arrhythmias: Implication for treatment. Epilepsy Behav. 2019; 97:304-312.
10. Katsiki N, Mikhailidis DP, Nair DR. The effects of antiepileptic drugs on vascular risk factors: A narrative review. Seizure. 2014;23(9):677-684.
11. Brodie MJ, Mintzer S, Pack AM, et al. Enzyme induction with antiepileptic drugs: Cause for concern? Epilepsia. 2013;54 (1):11-27.
12. Patorno E, Glynn RJ, Hernandez-Diaz S, et al. Risk of ischemic cerebrovascular and coronary events in adult users of anticonvulsant medications in routine care settings. J Am Heart Assoc. 2013;2(4):e000208.
13. Renoux C, Dell'Aniello S, Saarela O, et al. Antiepileptic drugs and the risk of ischaemic stroke and myocardial infarction: A population-based cohort study. BMJ Open. 2015;5 (8):e008365.
14. Chen Z, Liew D, Kwan P. Excess mortality and hospitalized morbidity in newly treated epilepsy patients. Neurology. 2016;87 (7):718-725.
15. Lee-Lane E, Torabi F, Lacey A, et al. Epilepsy, antiepileptic drugs, and the risk of major cardiovascular events. Epilepsia. 2021;62 (7):1604-1616.
16. Josephson CB, Wiebe S, Delgado-Garcia G, et al. Association of enzyme-inducing anti-seizure drug use with long-term cardiovascular disease. JAMA Neurol. 2021.