Journal of Pre-Clinical and Clinical Research, Vol 1, No 1, 006-008
www.jpccr.eu

REVIEW

Clinical considerations on the relationship between epilepsy and cardiovascular diseases

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Abstract: There have been reports regarding higher risk of unexpected death in epileptic patients. The aim of this review is to investigate causes of epilepsy-related death with special attention to cardiovascular mechanisms. Due to their high incidence among the general population, epilepsy and cardiovascular diseases are likely to coexist in a certain proportion of patients. The effect of calcium channel antagonists – representing drugs commonly used in cardiac pathology – on seizure control is also discussed on the basis of available experimental data.

Key words: epilepsy, cardiovascular diseases, sudden unexpected death, calcium channel antagonists

INTRODUCTION

Epilepsy is a chronic neurological condition, the incidence of which is determined at 0.5 -1% among the general population. The more advanced the age of the population investigated, the higher the number of people affected. It is estimated that approximately 50 million patients worldwide are diagnosed with epilepsy [1].

The number of people developing cardiovascular diseases has been on the increase. This trend reflects negative life style changes occurring in societies of rapidly developing and developed countries. Cardiological conditions are nowadays considered the leading cause of death in the modern world. According to data available for European countries, including Poland, the average incidence of arterial hypertension is assessed at 30%, with this percentage value being doubled in the population over 60 years of age [2]. The incidence of coronary artery disease depends on gender and age. In some populations, even every fifth male aged 65-74 suffers from this condition, with an average of 30-40 thousand cases in 1 million among the general population [3]. No reliable data are available for arrhythmia.

There is well-documented evidence which suggests that epilepsy is linked to a higher risk of death, including that from cardiac origins [4]. Moreover, considering the high distribution of cardiovascular pathology, it seems quite probable that some of these diseases may be diagnosed in epileptic patients.

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Received: 15 May 2007; accepted: 30 June 2007

TARGETING CALCIUM CHANNELS IN CARDIOLOGICAL DISORDERS AND EPILEPSY

Calcium channel antagonists (CCAs) represent one of several classes of medications commonly used to address various cardiological conditions, e.g. arterial hypertension, coronary artery disease, supraventricular arrhythmia, arterial pulmonary hypertension, or rapid ventricle response in atrial fibrillation [5-7]. CCAs block mainly L type voltage dependent calcium channels and, accordingly, produce a negative inotropic effect, dilation of peripheral vascular system and offer antiarrhythmic properties [8]. The influence of CCAs on the heart and vessels is unbalanced, depending on the class according to chemical classification. Diltiazem and verapamil have a greater effect on the heart, whereas dihydropyridine derivatives, representing the second class of agents under discussion, target the peripheral circulatory system to a far greater degree [9].

In neurons, all types of calcium channels have been identified, including the L type. Fox et al have documented that physiological neuronal transmission is accomplished using mainly N type calcium channels, whereas the sustained depolarization, as seen in seizures, involves L type calcium channels [10]. Because of the fact that CCAs alter intracellular calcium ion homeostasis, there have also been trials to use these drugs in anti-seizure treatment [11-13]. It is hoped that this treatment strategy will prove most beneficial for patients with concomitant cardiovascular disease and epilepsy.

CALCIUM CHANNEL ANTAGONISTS AND EPILEPSY

Contemporary guidelines on epilepsy management point to the necessity for satisfactory seizure control, which is clinically manifested by the seizure-free state [14]. Unfortunately, despite remarkable advances in the field of epilepsy research, novel antiepileptic drugs (AEDs) and new concomitant

treatment strategies, this goal is still beyond the reach of medicine.

Experimental data demonstrate that CCAs have unbalanced effects on the anti-seizure properties of AEDs. Initial experimental evidence, based on administering AEDs and CCAs, e.g. niguldipine, nifedipine, amlodipine or verapamil in animals, appeared encouraging to a large extent [15-18]. Some authors, in contrast, report a lack of anti-seizure efficacy of such an add-on treatment strategy; moreover, pro-convulsive action was reported in the case of niguldipine administered in combination with carbamazepine or phenobarbital in amygdala-kindled rats [19]. The safety of combined treatment with CCAs and AEDs in patients with epilepsy and cardiac disease is still unknown, however. Epilepsy significantly impairs the quality of life [20-21]. From a patient's perspective, the introduction of CCAs must not impair epilepsy control. The potential adverse effect of concomitant treatment with AEDs and CCAs should not be underestimated since experiments in the preclinical phase produced conflicting evidence. The value of flunarizine in clinical tests also seems unclear [11, 22].

Nowadays, the significance of evidence-based medicine for clinical practice cannot be questioned. Meanwhile, there is no ample data identifying the best therapeutic approach to epileptic patients diagnosed with concomitant cardiovascular disorder. Moreover, the data obtained from animal studies cannot simply be extrapolated to clinical conditions due to different pharmacokinetic parameters [23]. Undoubtedly, the combined use of AEDs and CCAs requires further detailed investigation and is of crucial importance for the safety of patients diagnosed with epilepsy and cardiovascular diseases, and who require chronic treatment with both AEDs and CCAs. An adequately careful approach to this group of patients and scrupulous analysis of clinical results is required.

UNEXPECTED SUDDEN DEATH IN EPILEPSY

Another clinically interesting aspect of the relationship between epilepsy and cardiovascular system pathology is the observation regarding the higher incidence of sudden unexpected death in patients presenting seizures and cardiological diseases, when compared to the general population. This risk was assessed at 23.7 fold higher, and in young individuals seemed even up to 40 times that for healthy people [4, 24]. In an overwhelming number of cases that have been studied thoroughly, the deaths occurred during or shortly after seizure attacks. The mechanism of death proved to be predominantly associated with cardiovascular system pathology [25]. The leading causes involved complex ventricular arrhythmia (dependent on autonomical neuroregulatory dysfunction), the proarrhythmic effect of AEDs and myocardial damage. Other potential factors that were raised encompassed the critical increase in blood pressure, hypoxia and obstructive apnoe. In addition, some authors have suggested the role of electrolyte disturbances, i.e. hyponatremia and hyperkalemia as cardiotoxic factors [26-31]. The aforementioned hypothesis was documented in animal models of epilepsy [32]. Oxcarbazepine treatment is indeed associated with hyponatremia and the incidence of this adverse event is as high as 25% in some reports [33]. This observation seems quite important from a clinical perspective, since administering diuretics to patients treated with oxcarbazepine may induce further sodium loss, and potentially lead to arrhythmia or conductance disturbances. For this reason, assessment of serum sodium concentration in these patients is vital, especially in the elderly [34].

Data regarding epilepsy-related death point to severe arrhythmias, including ventricular tachycardia, ventricular fibrillation and asystolia as the leading causes of these fatalities. Arrhythmia is considered the consequence of seizures or may be dependent on the proarrhythmic effect of AEDs [29, 35, 36].

There is ample evidence to suggest that pathological neuronal activity in specific areas of the brain triggers tachy- or bradyarrhytmias. The susceptible anatomical structures involve the insular cortex and certain regions of the frontal cortex [37]. The initial reports regarding the proarrhythmic effect of carbamazepine were not finally documented in controlled clinical trials. Only a slight negative impact on the overall incidence of death was reported for this drug [38]. It should be stressed, however, that in the case of a majority of available AEDs no such investigations were carried out; objective observations in this respect are therefor lacking. Only a few agents representing new generation AEDs (e.g. lamotrigine) were proved to produce no significant effect on the incidence of cardiovascular events in patients [30, 39].

IMPACT OF CARDIOVASCULAR DISORDERS ON EPILEPSY

The relationship between the primary cardiovascular disease and resulting epilepsy is also known, although less data is available. Arterial hypertension is associated with an increased risk for epileptic seizures. This does seem to be a direct finding, however. The reason for this observation is most probably a link between epileptogenesis and episodes of brain stroke and intracranial hemorrhage, representing complications of arterial hypertension. It is estimated that in up to 50% cases of epilepsy, a previous brain damage of vascular origin can be traced back in the history. In patients who developed brain stroke, arterial hypertension is considered an indirect risk factor for epilepsy [40].

CONCLUSIONS

Considering the crucial role of the calcium ion in both the physiological and pathological function of the central nervous system, as well as the cardiovascular system, it is extremely difficult to predict all the potential interactions and resulting clinical effects when combining CCAs and AEDs. Further investigation is necessary to identify clinically important relations between these systems with respect to management of epilepsy and cardiovascular diseases. The complexity of these interactions can be demonstrated by the fact that some cardiovascular effects are mediated by the function of the nervous system.

ACKNOWLEDGEMENT

This review was partially supported by Grant No. 2 P05D 096 29 from the Polish Committee for Scientific Research.

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