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Epilepsy Treatment in Patients with Heart Disease

*Scott Mintzer, MD**

Address
*Jefferson Comprehensive Epilepsy Center, Department of Neurology, Thomas Jefferson University, 908 Walnut Street, 2nd Floor, Philadelphia, PA 19107, USA
Email: scott.mintzer@jefferson.edu

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Abstract

Purpose of review This review highlights issues pertaining to the treatment of seizures in patients with cardiac disease. These fall into two categories: impacts upon the native disease — primarily an issue with coronary artery disease and arrhythmia — and drug interactions, which are important in all types of cardiac disease.

Recent findings A sizeable body of evidence indicates that enzyme-inducing anti-seizure medications (EIASMs) increase serum lipids and other serological and surrogate markers of vascular risk. A recent large epidemiologic study confirmed that patients treated with EIASMs are at significantly increased risk for cardiovascular disease. A recent Food and Drug Administration (FDA) alert highlighted the potential risk of arrhythmia in lamotrigine-treated patients with underlying cardiac disease; however, subsequent investigations have yielded, at best, only modest support for this concern.

Summary EIASMs are poor choices for patients with cardiac disease due to their propensity to cause drug interactions, and the multiple lines of evidence suggest that they exacerbate coronary artery disease. The FDA and epilepsy societies have recently highlighted the potential for exacerbation of arrhythmia with the use of lamotrigine; however, data to support this appears marginal, and more work is needed.

Introduction

Diseases of the heart are common in the general population, and as a consequence, anyone who treats seizures will frequently find themselves doing so in the context of cardiac disease. There are a number of important considerations that arise in doing so, depending upon both the nature of the cardiac disease and the nature of the epilepsy.

In this review, I will discuss the main of these considerations, with the goal of highlighting treatment options which may exacerbate heart diseases or adversely react with their treatments. The major categories of cardiac disease will be considered individually, though the reader should keep in mind that certain considerations will apply to more than one disease, given commonalities in physiology and drug treatment.

Coronary artery disease

Perhaps the most common of the cardiac diseases seen in medical practice, atheromatous impingement of the coronary arteries, with or without frank myocardial infarction, is the subject of a great deal of medical attention and effort, particularly in people aged 50 or more. As incident epilepsy is very common in older people, this is a common co-morbidity in practice, and there are two major considerations to be aware of in treating such patients, both of which relate to the effects of enzyme-inducing anti-seizure medications (EIASMs).

The first consideration is to avoid epilepsy treatments that will exacerbate the underlying condition. There is now a substantial body of evidence indicating that phenytoin (PHT) and carbamazepine (CBZ) significantly increase total cholesterol, as well as atherogenic lipid fractions (i.e., low-density lipoprotein cholesterol, triglycerides). This has specifically been shown not to occur with a number of other seizure medications, including levetiracetam, lamotrigine, zonisamide, topiramate, and lacosamide [1–4]. There is conflicting data regarding oxcarbazepine's effects on lipids [5–7]. It may occur in a mild but clinically unimportant fashion with eslicarbazepine [8]. Thus, it is highly likely that the hepatic enzyme induction properties of CBZ and PHT are responsible for these effects. This has been postulated to perhaps relate to effects on CYP51A1, a key enzyme in the cholesterol synthetic pathway, but this hypothesis has not been directly tested [9]. In addition to their effects on cholesterol, PHT and CBZ have also been shown to significantly elevate lipoprotein(a) and C-reactive protein, each of which is correlated with risk of myocardial infarction. They may also elevate homocysteine, another vascular risk marker, though the data on this is not fully consistent [10]. While there is little specific data, it is likely that phenobarbital and primidone have similar effects on lipids and other vascular risk markers, as these are also very potent, broad-spectrum hepatic enzyme inducers. A recent paper demonstrated the expected outcome of these changes: that patients treated with EIASMs have a significantly increased risk for cardiovascular disease [11••]. It bears noting, however, that the data on this issue are not entirely uniform [12•].

The second consideration for patients with coronary artery disease (CAD) pertains to drug interactions, and once again, it is mainly the same culprits: the enzyme-inducing ASMs CBZ, PHT, and barbiturates. These agents induce

the metabolism of a host of co-medications, among which are most of the HMG-CoA reductase inhibitors ("statins") that represent a mainstay of therapy for hyperlipidemia and secondary vascular disease prevention. The degree of increase in statin metabolism caused by EIASMs is very substantial, with studies showing reductions in statin exposure of 50–75% [13, 14]. This effect, combined with the aforementioned lipid-elevating properties of the drugs, results in a "double whammy" for patients with CAD or hyperlipidemia; the drugs will substantially elevate lipids, and then undermine the major drugs used to treat them. Interestingly, eslicarbazepine, a relative of CBZ, also has a substantial pharmacokinetic interaction with statins, but does not appear to impact their lipid-lowering effects; the reason for this remains to be elaborated [8].

The upshot of these effects is that CBZ and PHT (along with the barbiturates) are poor choices for patients with CAD and should be avoided, particularly with all the other equally-effective options currently available. A slightly stickier question is what to do with patients already on these drugs who develop CAD; this author favors switching them to alternative agents to avoid the aforementioned complications of enzyme induction (and many others besides). This is an easy decision when seizures are not controlled, or when the patient has other side effects. In a well-controlled patient, the risk of seizure recurrence with a medication switch is, of course, always a concern and has been surprisingly little-studied. The only data available in this regard suggests that the incremental risk of seizure recurrence when switching drugs in a seizure-free patient with focal epilepsy is around 14–17% [15, 16]. This is just high enough to be worth considering, yet just low enough to establish that the large majority of patients will have no problems. Engaging such a patient in a risk–benefit discussion is warranted.

Congestive heart failure

The end result of many cardiac disease pathways, congestive heart failure (CHF) is also extremely common in middle-aged and elderly patients, and, like CAD, will therefore be seen commonly as a co-morbidity with epilepsy in this age group. There are no ASMs that exacerbate the underlying condition itself, but CHF is treated with a plethora of medications, and the potential for interactions with some of these must be kept in mind.

Angiotensin receptor blockers are mainstays of therapy in CHF; losartan, among the most commonly used of these, will have its metabolism induced substantially by treatment with the EIASMs [17], and valsartan might be similarly affected.

Blockade of beta-adrenergic receptors is a common strategy for afterload reduction in CHF. Several beta-blocking agents which are prominent in CHF treatment, including metoprolol, carvedilol, and bisoprolol, are hepatically metabolized and are likely to have their effects substantially reduced by co-treatment with an EIASM.

Digoxin, while much less used than in the past, is still part of the cardiologist's armamentarium for late-stage CHF. Induction of digoxin metabolism by

phenytoin has been known for decades [18] and, given the narrow therapeutic index of digoxin, necessitates careful level monitoring and dose adjustment.

Finally, an interaction of a different kind may occur with the use diuretics, which are, of course, fundamental to CHF therapy. The issue here is a pharmacodynamic one pertaining to serum sodium levels, which are frequently reduced by treatment with diuretics of all kinds. The carbamazepine "family" of drugs, which includes the former, its relative oxcarbazepine, and the also-related eslicarbazepine, can themselves produce hyponatremia (through a mechanism that was initially thought to be the syndrome of inappropriate antidiuretic hormone secretion (SIADH), but is in fact something different [19]). Hyponatremia with this group of drugs is more likely to occur, and to be more severe, in patients who have lower serum sodium at baseline [20], which is often the case in patients taking diuretics. This is most typically problematic with the use of oxcarbazepine, which causes hyponatremia more commonly than the other two. Hyponatremia with these drugs is also more commonly seen in elderly patients. These drugs are not contraindicated in diuretic-treated patients, but should be used with some caution and with attention to serum sodium levels as warranted.

Patients with severe CHF may be anticoagulated; this is addressed in the next section.

Valvular disease

Drugs do not themselves generally affect the heart valves; however, fenfluramine, once used as a weight-loss agent, was removed from the market for this indication because of its occasional tendency to produce aortic and mitral valve thickening and regurgitation. This is relevant to the current review because the drug has been subsequently revived as a treatment for Lennox-Gastaut and Dravet syndromes, two conditions in which seizures can be especially difficult to treat, such that the risk–benefit ratio may be appropriate even for such a noteworthy risk. It should be obvious, then, that such a ratio would be different in a patient who already has pre-existing disease of the aortic or mitral valves, and a decision about the use of this drug may need to be reconsidered accordingly.

A far more common consideration would be the potential for drug interaction with warfarin, which is a cornerstone of therapy for patients with mechanical valves (and sometimes for other valvular conditions). Carbamazepine clearly induces warfarin metabolism, which would render the patient vulnerable to clotting complications without careful warfarin dose adjustments [21]. Barbiturates may have a similar effect, though data on this is mixed [22]. Phenytoin has a very complex interaction with warfarin. On the one hand, like carbamazepine and barbiturates, it substantially induces warfarin metabolism; on the other hand, it may displace warfarin from albumin binding sites, and it also competes for sites on CYP2C9, which is a key metabolizing enzyme for both drugs, which effects would serve to increase warfarin exposure. The sum total of these interactions is quite unpredictable, and very close monitoring is necessary [21]. It is clear that the use of EIASMs

should be avoided in the context of warfarin treatment if at all possible. A recent study suggested that oxcarbazepine does not alter warfarin effects [22].

Arrhythmia

With regard to epilepsy treatment in the setting of cardiac arrhythmia, there are both potential drug interactions and effects on the underlying condition to be considered.

Many patients with arrhythmias receive anticoagulation, and potential interactions with warfarin are addressed in the above section. For atrial fibrillation, the direct oral anticoagulants (DOACs) are increasingly used. A recent review suggests the possibility of interactions between several of the DOACs and a number of anticonvulsants, some expected (e.g., phenytoin, carbamazepine) and some surprising (e.g., levetiracetam). The authors acknowledge that the quality of data in this realm is low overall, and that much more data is needed to clarify this [23].

Many antiarrhythmic drugs are hepatically metabolized and will therefore will have their levels reduced by the EIASMs (phenytoin, carbamazepine, and the barbiturates). These include the calcium channel blockers verapamil and diltiazem; the sodium channel drugs mexiletine, quinidine, disopyramide, and propafenone; and the multiple-action drug amiodarone. Some of these drugs are also induced by oxcarbazepine and eslicarbazepine, which have more modest enzyme-inducing activity than the full-fledged EIASMs; in some cases, this is a clinically notable effect, and in others it is of uncertain significance. Consultation of drug reference volumes is warranted for full details regarding this complex drug class.

Aside from drug interactions, certain ASMs which primarily work via sodium channels may alter cardiac conduction and produce arrhythmias in vulnerable patients. Phenytoin is officially classified as a class Ib antiarrhythmic agent and was for decades considered the standard treatment for digitalis toxicity; like any antiarrhythmic, it may have pro-arrhythmic effects, and caution must be used in patients vulnerable to certain arrhythmias. Interestingly, there is little to no evidence that carbamazepine contributes to cardiac arrhythmia, despite its pharmacologic effect on sodium channels and its structural similarity to the tricyclic antidepressants.

Lacosamide, a newer antiepileptic agent which enjoys extensive use, was found to increase the PR interval in clinical trials (but not the QT interval, as is seen with many drugs in other classes). Concerns were raised when, in a trial of lacosamide for the treatment of diabetic neuropathy, several patients experienced syncope; however, no connection was ever found between these syncopal events and any cardiac rhythm abnormalities. A recent literature review yielded a total of 17 case reports of lacosamide-related arrhythmias, among which there were 5 cases of ventricular tachycardia, 3 of complete heart block, and 3 of new-onset atrial fibrillation [24]. Assessment of causation in such cases is difficult, and more work is clearly necessary to clarify this, but in the meantime it seems prudent to exercise caution in patients in whom PR prolongation might create risk.

Finally, and most prominently, is a recent controversy regarding the arrhythmogenic potential of lamotrigine. In October of 2020, the US Food and Drug Administration (FDA) issued a warning after receiving reports of abnormal ECGs and cardiac symptoms in several lamotrigine-treated patients; they commissioned in vitro studies, which reportedly suggested "potential increased risk of arrhythmias" and recommended that lamotrigine be avoided "in patients with certain cardiac disorders or arrhythmias." A joint task force of the American Epilepsy Society and the International League Against Epilepsy examined the issue and recommended "that a cardiologist's opinion should be considered before starting lamotrigine in people with comorbid cardiac conditions." They also recommended that in patients above age 60, an ECG be performed when lamotrigine is initiated (reasoning that the very slow titration of the drug permitted this to be done concurrently, while the drug is being given at a very low dose). Presumably in deference to the task force, FDA subsequently revised its warning in March of 2021, rescinding its prior recommendation regarding avoidance of the drug.

Ingleby-Talecki et al. [25•] studied lamotrigine in vitro and found sodium channel effects similar to those of the Ib antiarrhythmics; they also found that changes in PR and QRS intervals on ECG were very modest, and not of clinical import to the general population, though it is conceivable that they might be relevant to those with advanced conduction disorders. Christensen et al. [26••] performed a large population study of around 92,000 new lamotrigine users and found no increase in cardiac morbidity or mortality, even in the subgroup of patients with pre-existing cardiac disease. Bunschoten et al. [27••], in a rapid review, found that in 12 studies of ECG abnormalities with the drug, 2 showed only small, non-meaningful changes, and 10 showed no alterations; however, they found the quality of evidence low and concluded that there was "insufficient evidence to support or refute" that LTG is associated with ECG changes. This important issue remains to be clarified further.

Summary

Various considerations pertain when treating epilepsy in patients with cardiac disease, depending upon the specific conditions, and the specific medications they may be taking for the treatment of said conditions. The biggest take-home points in this regard are as follows:

- Seizure medications which induce hepatic enzymes — carbamazepine, phenytoin, and barbiturates — should largely be avoided in patients with cardiac disease due to their significant propensity to produce drug interactions. They should especially be avoided in patients with coronary artery disease owing to their demonstrated negative effects on serum lipids and other markers of vascular risk, which will exacerbate the underlying condition.
- Some caution should be exercised when using carbamazepine derivatives — especially oxcarbazepine — in diuretic-treated patients, due to the increased risk of significant hyponatremia.

- Concerns have been raised regarding the use of lamotrigine in patients at risk of cardiac arrhythmia, though the evidence supporting these concerns is mixed, and more clarifying work remains to be done.

Compliance with Ethical Standards

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interests
The authors declare no competing interests.

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- •• Of major importance

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Publisher's Note