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Review Article

Carbamazepine (Tegretol) –An half century of survival

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Abstract

Introduction: Carbamazepine (Tegretol®) (CBZ), has been available for half a century suggesting all that needs to be said has been said but it has truly withstood the test of time.

History revisited: CBZ was discovered during the research and development of imipramine, a tricyclic antidepressant and retains psychotropic benefits which are propitious in the treatment of epilepsy. CBZ has both standard antiseizure medication (ASM), adverse events (AEs), as well as idiosyncratic AEs that must be appreciated when using CBZ. Genotyping allows definition of those for whom CBZ is contra indicated. It can also exacerbate certain seizure types, such as generalised epilepsies, such as juvenile myoclonic epilepsy.

Risk/Benefit Ratio: Blood level monitoring of CBZ levels allows tailoring of treatment to the patient's needs and identifies both ASM causing toxicity or non-compliance/non-adherence, possibly before breakthrough seizures occur. Medication interactions, consequent to liver enzyme induction, need to be acknowledged and monitored.

Conclusion: It follows that with adequate preparation and understanding, CBZ remains a favoured ASM in the treatment of focal epilepsy. As with any medication it is imperative to understand the 'pros and cons' but, with due diligence, CBZ deserves to remain at the top of the list for quite some time to come.

INTRODUCTION

Carbamazepine (Tegretol®) (CBZ), has been around for half a century, having first been written up in the early 1960's [1], initially for the treatment of tic douloureux [1], and later for the management of what is now referred to as focal epilepsy [2], in the new classification [3]. When asked to prepare an overview of CBZ, the initial impression is that all that needs to have been said has been said [4] but, were that the case, the invitation to provide a review article would not have arisen. What follows is the idiosyncratic opinions of the author whose longevity has matched that of CBZ and who still favours it as the go to drug both for focal epilepsy and for some pain syndromes.

HISTORY REVISITED

CBZ, like so many land mark discoveries in medicine, was the product of an error within the laboratory and was found during the research and development of imipramine (Tofranil®) [5], a tricyclic antidepressant, and, while this may not seem too exciting a statement, it does have real ramifications for an epileptologist. Epilepsy is a depressing diagnosis [6], for which many of the available medications, used to treat seizures, may add to depression, such as levetiracetam (Keppra®) [7]. CBZ has the inherent properties of also offering antidepressant features which have withstood the test of time [8], and may offer a modicum of hope to the person with epilepsy (PWE).

Having painted a glowing picture, one must also acknowledge that no medication is without unwanted adverse effects (AEs), and CBZ is no exception to this rule. The often cited, common AEs that can occur with most antiseizure medications (ASMs), include: skin rash [9], nausea and vomiting [10], fatigue and lassitude [11], incoordination [12], and possible photosensitivity [13]. There are also specific, idiosyncratic AEs which accompany the use of CBZ, such as: neutropenia [14], thrombocytopenia [15], aplastic anaemia [16], enzyme induction with potential drug interactions [17,18], and genotypically defined drug sensitivity [19].

Genotyping may also be seen as a positive for CBZ, as it allows pre-dose definition of those for whom CBZ is contraindicated [20,21], including patients with Han Chinese ancestry or a genetically defined subset of Caucasians, thereby allowing genopharmacology. This represents the start of personalised medicine and the definition of which ASM is contraindicated in which type of patient. It is too early to determine how far this development will evolve but it is the definitive start of genotypical pharmacology and the direct application of genotyping to clinical medicine, reflective of the saying, "from bench to patient with translational application of science.

CBZ may exacerbate some seizure types, such as generalised myoclonic seizures [22], and is contraindicated for generalised epilepsies [23], namely those seizures without focal onset, It still remains an affective first-line treatment for focal epilepsy [24] , despite its half century of existence. So good is its track record

that it remains the ASM of choice against which novel ASMs are compared when treating focal epilepsy. In head-to-head trials, no ASM has proven more efficacious than is CBZ, in the treatment of focal epilepsy [25-29].

RISK/BENEFIT RATIO

CBZ blood levels are easily obtainable which offers another positive to the tailoring of treatment to each patient's needs. While many of the newer ASMs argue the opposite, claiming economic benefit from not using therapeutic blood level monitoring, this is a fallacy which should be revisited. The use of blood level determination gives rapid feedback, when trying to treat cluster seizures, as it allows necessary feedback that adequate doses have been supplied [30]. While there is no parenteral formulation of CBZ, it can be effectively delivered per rectum, using the oral syrup formulation, with blood level monitoring to determine adequate dosing [31]. Various blood levels of CBZ can be sought, acknowledging that one can measure the total blood level and/or the free, unbound fraction of CBZ [32], or even the epoxide metabolite, if required [33].

There is a slow release formulation of CBZ making twice daily dosing very convenient [34], allowing pre-dosage, trough level determination of blood level easily obtainable, without excessive inconvenience for the patient(s). Use of therapeutic monitoring can also improve compliance as it can identify non-compliance, when levels fall, even if the levels remain within the therapeutic window [4]. If the patient presents with symptoms of ASM toxicity, easy access to blood levels, especially the full suite of total, free (unbound fraction), and metabolite may better facilitate identification of the offending ASM thereby assisting in treatment modification. This has special relevance when CBZ is added to previous treatment with phenytoin (PHT), due to competitive protein binding [4]. The easiest approach would be to consider that as CBZ was the latest addition it must be the toxic ASM but adding CBZ to PHT can actually lower total PHT levels but, due to competitive protein binding, it could well be the free fraction of PHT that is the culprit and reduction in PHT dosage may be the appropriate response, especially acknowledging the pharmacokinetics of PHT [4].

There are well recognised drug interactions, such as CBZ halving the half life (t½) of lamotrigine, from 30 to 15 hours [35], or increasing the metabolism of the oral contraception pill [36]. Similar interactions can occur with anticoagulation, reducing the efficacy thereof and requiring increased dosage [37]. So long as the prescriber is aware of such interactions, due diligence should apply and monitoring blood levels, both of CBZ and concomitant medications, will obviate any untoward complication(s) and facilitate optimal patient care. These interactions are as a consequence of liver enzyme induction which may be mistaken for liver toxicity and offer a trap for young players [4]. CBZ also may cause fluid retention resulting in hyponatraemia [38], which could, itself, be epileptogenic [39], but is easily managed with fluid restriction rather than increasing sodium in the diet or the use of diuretics [40].

CONCLUSION

It follows that with adequate preparation and understanding, CBZ remains a favoured ASM in the treatment of focal epilepsy. As with any medication it is imperative to understand the 'pros and cons' but with due diligence CBZ deserves to remain at the top of the list for quite some time to come.

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