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The Use of Drug Levels to Treat Cluster Seizures in Epilepsy Management

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Abstract

Introduction: Current attitude to epilepsy management avoids use of blood level determination, a position which may be appropriate in stable situations. Despite this, use of blood levels may have a definite role in managing cluster seizures.

Background: Cluster seizures are a medical emergency treated with short acting benzodiazepines (BDZ) and longer acting anti-epileptic medications (AEM). Blood levels of the longer acting AEM may assist management decisions.

Discussion: In an age of individualized patient care, it seems counterintuitive to treat cluster seizures, a medical emergency, with standard dosages and no laboratory evaluation. AEM blood levels allow confirmation of adequate dosage and repeated treatment if the levels are sub-therapeutic. It affords the patient and clinician added insight to improve patient care.

Keywords: Cluster seizures; Individualised care; Emergency; Blood levels

Introduction

Current opinion in the treatment of epilepsy is to avoid the use of blood level determination and to rely almost exclusively on the clinical picture [1]. This presumes a stable patient without fluctuations in seizure expression or changes in anti-epileptic medications (AEM), which may not always be apparent, as may be the case with generic substitution [2].

Having achieved steady state in seizure control and patient management, it seems reasonable to avoid blood level determination of AEM when the clinical picture is stable. The role of AEM blood levels is to determine possible causes for changed patient status, should seizures occur; or to redefine the situation if the therapeutic regime has been changed, either by altered doses or altered medications. AEM blood levels may also be used as an adjunct to assess patient compliance [3].

An area in which AEM blood level assessment has been largely overlooked is in the acute management of poorly controlled cluster seizures, akin to status epilepticus. This paper will provide cogent argument for the use of AEM levels in the management of cluster seizures.

Background

Cluster seizures are often the basis for medical emergency team attendance within the hospital setting [4,5]. Such patients are often administered a short-acting benzodiazepine (BDZ), such as midazolam [6] and then loaded with a long-acting AEM, such as phenytoin (PHT) [7]. The use of the long-acting AEM is to protect the patient, once the shorter-acting BDZ has been eliminated.

While the use of PHT may be debated [8], the concept of patient protection with a long-acting AEM is most reasonable. The emergency team may then assume that this approach has provided adequate patient care, without the need for AEM blood level determination to indicate that adequate loading has actually occurred.

PHT is no longer a first line AEM [9] with carbamazepine (CBZ) being the gold standard for partial seizures/focal epilepsy [10]. There is no formulation for parenteral route administration of CBZ, although it is possible to achieve rapid therapeutic concentrations using per rectal (PR) administration [8]. There are formulations of valproate (VPA), levetiracetam (LEV) and lacosamide (LCD), which can be administered intravenously to give loading doses.

There is an accepted therapeutic range for VPA [11], which is a broad-based spectrum AEM and could be used to provide longer-term protection, following short-acting BDZ. The author is also assessing AEM levels of LEV, and while it is too early to be certain, clinical impression suggests a level of between 20 to 40 mg/L may be appropriate. Should CBZ be administered PR then blood level determination can be used to establish that a therapeutic level has been achieved.

Discussion

Cluster seizures represent a group of epileptic seizures that demand acute intervention to both stop the current seizure activity and to protect against further seizures, if possible. Cluster seizures represent an emergency situation akin to status epilepticus [12]. While the most common cause for acute exacerbation of seizures is non-compliance with established treatment [13], cluster seizures may also occur as a consequence of other factors, such as stroke [14], or infection [15] in previously undiagnosed epilepsy.

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The current approach of BDZs complemented by long-acting AEM is rational [8] but failure to assess AEM levels in this situation also fails to recognise idiosyncratic response to AEM loading. Patients may require larger doses to achieve therapeutic levels of AEM, especially with confounding variables, such as the use of concomitant medications or comorbidities.

It seems counterintuitive to use a standard loading dose and to ignore interpatient variability where most acute medical facilities have the capacity to measure AEM levels, especially for VPA or CBZ. These levels can be measured and, where the level is found to be sub-therapeutic, a further loading bolus could be delivered and the process repeated until a therapeutic level is achieved. Only with therapeutic levels can the clinician truly have confidence that the provision of long-acting AEMs delivers patient protection once short-acting BDZs have been eliminated. Perhaps the most realiable AEM therapeutic range attaches to PHT, which is still the widest used AEM within the context of management of status epilepticus [16] and cluster seizures [17]. PHT has saturable metabolism, which is highly sensitive to interpatient variability [18]. Determination of PHT levels is both relatively inexpensive and rapid [19].

Where the measurement of AEM levels is readily available and its determination would add an extra dimension of patient protection, it is difficult to understand why this technology is not more widely adopted in the modern management of emergency treatment, as practiced with cluster seizures. In an age where tailored patient care should be the gold standard, it is difficult to explain why such a simple tool is not more widely adopted to improve patient supervision within the emergency setting. Adaptation of results of AEM levels, aiming for an accepted therapeutic window, at least for PHT, VPA or CBZ, would afford the patient added protection, well beyond the period in which a single bolus effect might last. It offers the patient the wherewithal to be transferred from emergency dosing to routine management with a more informed understanding of how that individual patient responded to the AEM given as a bolus dose. It seems reasonable to assume that where it required multiple doses, delivered by bolus, to achieve therapeutic levels, the patient may require larger maintenance doses in routine care.

Having achieved a therapeutic level for emergency management, it is appropriate to transfer the patient to routine oral maintenance dosing of the proband AEM. The fact that PHT is no longer a first line AEM [9] is solid argument against its use in the emergency setting, appreciating that long term management with a first line AEM should be the goal. This is the topic of another thesis. For the purposes of this debate, transfer from bolus AEM, to maintenance AEM, will be more reliably executed with some better appreciation of patient metabolic response to bolus loading. AEM blood level determination provides such appreciation and should be used in the days following transfer to oral dosing. The choice of dose of AEM should adopt an individual approach, based on levels following bolus administration but, as already stated, the expression of cluster seizures may be consequent to confounding factors, such as stroke or infection. Once these variables have been appropriately managed, it is possible that AEM metabolism may also be modified. It is within this context that use of AEM blood level determination, during this period of change, will add a further dimension to the more scientific management of individualized patient care.

In conclusion, it is correct that a patient with well controlled epilepsy, in whom the dosage of AEM is stable and the patient is both seizure free and devoid of adverse events, does not require AEM blood level evaluation. In the patient with cluster seizures, in the acute setting of poorly controlled epilepsy in a potentially emergency situation, the use of AEM levels provides both the patient and clinician an added layer of protection. The use of AEM levels, within this context, confirms when the patient has achieved a therapeutic dosage; allows repeated dosing to achieve such a level; and offers some insight into the informed choice of a long term strategy to better manage that individual patient's epilepsy, at least in the acute phase over the next few days after the cluster of seizures occurred.

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