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CASE REPORT

Value of therapeutic drug level monitoring and unbound (free) levels☆

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Summary Therapeutic drug monitoring (TDM) has declined with newer anti-epileptic drugs (AEDs) having no therapeutic window. Use of unbound (free) fraction has almost completely disappeared. The case reported highlights its importance and offers sound reason for its retention.

A 66-year-old Caucasian man with known epilepsy was admitted with vomiting, ataxia and nystagmus presumably due to AED toxicity. Medications included valproate (VPA) 1 g bd; phenytoin (PHT) 200 mg tds; carbamazepine (CBZ) 400 mg mane, 200 mg midi, 400 mg nocte; levetiracetam (LEV) 250 mg bd. Initial AED-TDM revealed total serum levels of CBZ: 27 μmol/L; PHT: 37 μmol/L; VPA 499 μmol/L, therapeutic or subtherapeutic. Free levels were subsequently measured demonstrating CBZ: 8.2 μmol/L; PHT: 5 μmol/L; VPA 93 μmol/L. Consequently, VPA was initially omitted and dosage reduced with cessation of toxicity. AED regimen was greatly simplified and remained efficacious.

This case highlights the value of TDM with polypharmacy and suggested AED toxicity. Total AED levels failed to identify the cause, which the unbound, free fraction identified. While total PHTwas borderline subtherapeutic (37 μmol/L; range: 40—80) the free level was therapeutic (5 μmol/L; range: 4—8) and while VPA was therapeutic (VPA 499 μmol/L; range: 300—750) the free level was supratherapeutic (93 μmol/L; range: 30—75). Acknowledgement of discordance between total and free levels for highly protein-bound AED is highlighted.

Introduction

The use of therapeutic drug monitoring (TDM) of anti-epileptic drugs (AEDs) in the treatment of epilepsy, starting with phenytoin (PHT), has been recognised for almost 50 years.[1] By the 1970s, the use of total drug level monitoring was widely accepted as adjunctive to manipulating medications in the management of epilepsy,[2] based on the

☆ This case report has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

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expectation that the concentration of AED within plasma reflected therapeutic efficacy.[3]

The relevance of the free or unbound fraction of the AED PHT was recognised in 1960.[4] The role of total and free AED serum concentrations was further investigated in the mid-1980s[5] demonstrating that there existed a 30% discordance between the total and free AED level results for PHT and valproate (VPA) (known to be 90% protein bound and 10% free under normal circumstances) and a 20% discordance between total and free drug levels for carbamazepine (CBZ) (known to be approximately 75% protein bound and 25% free under normal circumstances).[5]

More recently, the cost effectiveness and appropriateness of the use of TDM has been questioned,[6,7] particularly with the newer AEDs where it has been shown that such monitoring need not correlate with efficacy.[7–10]

The following case reports the use of discordant free fraction measurement of AED in determining the appropriate medication to be altered in order to achieve optimal patient care and reviews the role of total and free AED level measurement in the treatment of epilepsy.

Case report

S.M., a 66-year-old Caucasian man with known epilepsy, ischaemic heart disease, hypertension, hyperlipidaemia, oesophageal reflux and hearing loss presented to the Emergency Department with vomiting, diarrhoea, and unsteady gait. His epilepsy was controlled with PHT 200 mg tds; VPA 1 g bd; CBZ 400 mg mane, 200 mg midi, 400 mg nocte; and levetiracetam (LEV) 250 mg bd. Other medications included aspirin 100 mg daily; clopidogrel 75 mg midi; simvastatin 40 mg nocte; metoprolol 100 mg bd; perindopril 8 mg mane; amlodipine 10 mg mane; frusemide 40 mg mane; and spironolactone 25 mg mane. On examination he was found to have bilateral horizontal nystagmus and significant ataxia.

The clinical picture was diagnosed as consistent with AED toxicity, however, total serum AED levels were measured which demonstrated sub-therapeutic PHT (37 μmol/L; range: 40–80), and therapeutic CBZ (27 μmol/L; range: 25–50) and VPA (499 μmol/L; range: 300–750). LEV levels were unavailable within the hospital due to non-existence of an accepted therapeutic window. These results contradicted the diagnosis of AED toxicity, despite his clinical presentation and the absence of a viable alternative diagnosis.

The treating neurologist requested measurement of free AED levels to clarify the cause of his suspected toxicity, a request that was met with significant resistance from the laboratory responsible for measuring same. Following discussions free levels were measured and revealed a supra-therapeutic level of free VPA (93 μmol/L; range: 30–75); and therapeutic levels of free PHT (5 μmol/L; range: 4–8) and free CBZ (8.2 μmol/L; range: 6–13). On the basis of these findings and the presenting symptoms being typical side effects of VPA, VPA was considered the most likely cause of S.M.'s toxicity and was initially omitted for one day and then reintroduced at a reduced dosage of 500 mg bd. This led to the prompt cessation of his symptoms. Over the subsequent days, in order to reduce the complexity of his antiepileptic regimen and reduce the potential for drug interactions, PHT and LEV were withdrawn while the administration of CBZ was simplified to 400 mg mane and 600 mg nocte. S.M. remained seizure free and was discharged home 6 days later with a much simplified AED regimen and morning drug fasting blood samples revealing therapeutic levels of VPA (total 351 μmol/L, free 31 μmol/L) and CBZ (total 30 μmol/L, free 8.2 μmol/L). S.M. was last seen 8 months post-discharge and has not had another episode of AED toxicity to this date.

Discussion

While TDM has been used for decades in the management of epilepsy,[2,3,11] its use has been declining in recent years.[6,7,12] The basis for the reluctance of the pathology department to offer further AED level determination, in the case of S.M., was acknowledgement of the recent literature which questioned the relevance of TDM, particularly with reference to free fraction determination.[7,9,10,13–16] Free fraction determination has never been as widely adopted, as has total serum AED level determination,[17–19] and the fact that S.M.'s total AED levels were either within the mid-to-low therapeutic range (regarding VPA and CBZ) or in the sub-therapeutic domain (as was the case with PHT) was proffered as the rationale for the initial refusal to perform free fraction determination. It was accepted that there was no agreed therapeutic window for, nor capacity to measure, LEV levels in the hospital but the dosage of same, at 250 mg twice daily, was thought to be so low as to make it an unlikely cause of the toxicity, recognising that the mean dosage of LEV was 3000 mg in pivotal clinical trials.[20] The pathology service failed to acknowledge the potential discordance between total and free levels of AED, with complete reliance on total

levels which, in this case, failed to explain the clinical picture.

With the introduction of newer AEDs, where TDM has been show to be less beneficial,[7,9,10] as in the case of gabapentin, the decline in TDM has been accelerated to the point that emerged in the case of S.M. where the literature was used as the basis for initial refusal to offer the service. As a result of the current trends, many doctors, especially junior house staff, often do not understand the clinical use and value of TDM and thus will be less likely to request these tests, particularly measurement of free levels, which proved invaluable in the management of the toxicity encountered by S.M.

This case highlights the value of TDM in the setting of polypharmacy and clinical evidence of AED toxicity. In such a situation there are complex drug interactions, affecting both AED metabolism[21–23] and potential for protein binding[17,23] which may make it impossible to identify which of the AEDs is the cause of the patient's symptoms. S.M.'s case shows that, with therapeutic or subtherapeutic total AED levels, they can fail to identify the cause of toxicity, in which setting the measurement of the free, or unbound, fractions may be invaluable to identify the causative AED, namely VPA which showed a mid-range therapeutic total level of 499 μmol/L but a supratherapeutic free level of 93 μmol/L. There are a number of possible explanations for the elevated valproate level in this case. Firstly valproate demonstrates non-linear pharmacokinetics with concentration dependent plasma protein binding. If the protein binding sites are saturated, the free valproate level can rise rapidly. Secondly, there are a number of drug interactions in play. Valproate and phenytoin may displace each other from protein binding sites, while aspirin also has this property as well as inhibiting the metabolism of valproate.

The potential discordance between total and free AED levels[5] underlines the value of measuring the free fraction levels in certain circumstances of TDM, as evidenced in the present case. This discordance, between total and free AED TDM, has been demonstrated previously, however, with the decline in use of TDM it is less well recognised by junior doctors and was therefore difficult to organise in the case of S.M. where its relevance was confirmed and greatly assisted patient care.

This case serves as a reminder that TDM, and in particular free AED level determination, has a valuable role in the clinical management of epilepsy, if used judiciously in circumstances where it may be the only means to identify which, of a variety of AEDs, is responsible for a particular clinical presentation.

Conflicts of interest

None.

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