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Short communication

Withholding the choice of sodium valproate to young women with generalised epilepsy: Are we causing more harm than good?

Tom B. Mole [a], Richard Appleton [b], Anthony Marson [c,*]

[a] Department of Psychiatry, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK
[b] The Roald Dahl EEG Unit, Paediatric Neurosciences Foundation, Alder Hey Children's NHS Foundation Trust, Liverpool L12 2AP, UK
[c] Division of Neurological Science, University of Liverpool, Clinical Sciences Building, Lower Lane, Fazakerley, Liverpool L9 7LJ, UK

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ABSTRACT

Purpose: Although sodium valproate (VPA) remains the most effective antiepileptic for generalised and unclassified epilepsies, clinicians may be failing to discuss this treatment option because of guideline misinterpretation. Current guidelines recommend caution regarding teratogenic risks but do not advocate absolute avoidance.
Method: We assessed VPA prescribing in young people attending a transition epilepsy clinic. We present six patients with idiopathic generalised epilepsy (IGE) in whom VPA had been initially avoided.
Results: Overall, the results were consistent with VPA's superior antiepileptic efficacy and ability to reduce harmful seizure-related complications. Young people denied of VPA showed prolonged periods of poor seizure control with medical, social and psychological complications. Following contraceptive counselling and VPA introduction, all six patients showed improved seizure control including seizure-freedom during follow-up of up to twenty-four months. There was also evidence of reduced seizure-related morbidity and improved educational and occupational functioning. Prior to referral, documentation revealed no discussion of VPA treatment options.
Conclusion: Failure to prescribe valproate for IGE, particularly when another first-line treatment has failed, may not be in a young woman's best interests-particularly when they are most vulnerable to sequelae from uncontrolled seizures. Indiscriminate avoidance of valproate needs to be recognised as a misinterpretation of current epilepsy guidelines as it may harm young people. Although the use of valproate demands careful consideration, there remains a strong case to always discuss this medication because of its efficacy and potential to reduce seizure-related harm. Patients must be allowed to make their own informed decisions about effective epilepsy treatments.

1. Introduction

Although sodium valproate (VPA) remains the most effective antiepileptic for generalised and unclassified epilepsies [1,2], current guidelines [3–5] appropriately recommend caution when prescribing the drug for young women of childbearing age. Lamotrigine and levetiracetam are commonly recommended alternatives largely because they are considered to have fewer and less severe adverse side-effects, including foetal teratogenicity. These treatment guidelines are principally informed by observational studies including data from pregnancy registers that show higher rates of major somatic malformations in pregnancies exposed to VPA, for example the EURAP registry [6] showed a rate of 5.6% with <700 mg valproate and 24.2% with >1500 mg valproate per day, 2.0% with <300 mg lamotrigine per day and 4.5% with >300 mg per day. Valproate is also associated with impaired cognitive development [7] in the absence of any foetal malformations.

Although lamotrigine may be safer in pregnancy, it is less effective in controlling most seizure types that occur in the idiopathic generalised epilepsies (IGEs) and specifically tonic–clonic seizures; the same is also true of topiramate. There are inadequate comparative efficacy data for levetiracetam. Prescribing a less effective treatment exposes the patient to a greater risk of continuing seizures [8], consequent risk of injury (including rarely, death) and psychological consequences and social disadvantage [9,10].

* Corresponding author. Tel.: +44 151 529 5770.
E-mail addresses: tm507@cam.ac.uk (T.B. Mole), A.G.Marson@liverpool.ac.uk (A. Marson).

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Guideline developers must weigh the risk:benefit ratio of treatments when writing their guidance. This is particularly challenging in this scenario as evidence about benefit and harm will come from many different sources. Guidance that is too risk-averse in terms of preventing teratogenicity might expose women to an increased risk of seizures, and particularly tonic–clonic seizures. In addition, the clinical interpretation and implementation of guidance also requires careful consideration and over-cautious interpretation might have the same effect. Finally, implementation is also limited by a paucity of data that identify the priorities and preferences of young women who are about to start treatment for epilepsy. Such issues highlight the need for examining significant sequalae when operationalising epilepsy guidelines.

2. Material and methods

We assessed the impact of treatment approaches for young people attending a transition epilepsy clinic. We report on six young people with an IGE seen in a specialist transition (teenager) epilepsy clinic in the UK accrued over 18 months [11]. None of the patients had achieved a seizure-free period of more than six months; all had received a range of anti-epileptic medications, either singly or in combination, but never VPA. Following discussion of the different treatment options with the young person and their family, all patients elected for a trial of VPA; six were converted to valproate monotherapy and one patient continued to receive valproate in combination with another anti-epileptic drug. Details of the six patients are shown in Table 1.

3. Case series

Five of the six patients had experienced specific adverse consequences from uncontrolled seizures. Prior to commencing VPA, Cases 3 and 5 had a protracted period lasting several years of uncontrolled seizures despite multiple trials of different high-dose monotherapies. Cases 2 and 3 had tried monotherapies and combination therapies and reported adverse effects including renal calculi and sedation. Two patients required acute medical intervention (Cases 1 and 4) for uncontrolled clusters of tonic–clonic seizures and two experienced mental health complications (Cases 3 and 5) that necessitated acute psychological support and psychiatric intervention.

All six patients demonstrated improved seizure control after commencing VPA, remaining seizure and complication-free throughout the short duration of follow up (4–24 months). Following seizure-cessation, social isolation and clinical depression reduced in Cases 3 and 5, school attendance improved in Case 3 and continuing higher education became a reality for Case 2. Adverse side-effects were experienced by Cases 2, 4 and 5 but these did not necessitate either a reduction in dose or withdrawal of the drug. Although data were unavailable on whether patients were sexually active or using contraception, all women after referral to the transition service routinely received documented nurse-led counselling on contraception and advice about pregnancy.

4. Discussion

All six patients experienced prolonged periods of poor seizure control and consequently suffered physical, psychological and social complications during treatment regimes that had excluded VPA. Following the introduction of VPA, seizure control improved in all six; all had achieved seizure freedom during the 4–24 month follow-up. None of the patients subsequently experienced any medical complications (including injuries) whilst on valproate and a number demonstrated improved psychosocial functioning. This would suggest that, had VPA been introduced earlier in their management, they would have experienced fewer, if any, medical and psychological consequences associated with poor seizure control. Clearly, this hypothesis cannot be proven. However, the superiority of VPA compared to other anti-epileptic medications in enabling seizure-freedom has been demonstrated in randomised trials. For example, alternatives to valproate such as lamotrigine and topiramate for generalised epilepsies are likely to bring an increased risk of treatment failure and seizures (hazard ratio 1.25 and 1.89 respectively for time to treatment failure) [1].

4.1. Uncontrolled seizures: significant medical, psychological and social complications

Medical complications associated with poor seizure control are well-recognised and include accidental injuries, death (including from sudden unexpected death in epilepsy [SUDEP] or suicide) and mental health disorders. Anti-epileptic regimes that optimise seizure control are considered likely to minimise the medical complications and maximise quality of life [10].

Generalised tonic–clonic seizures during pregnancy can lead to foetal loss through severe hypoxia, direct trauma and intracranial haemorrhage. Convulsive (tonic–clonic) status may be associated with foetal death in 50% of cases [12]. It is also possible that poorly controlled seizures could adversely affect psychomotor development of the child. Finally, poorly controlled seizures may also have financial consequences for the woman as well as the NHS and other healthcare institutions.

Three of our cases experienced significant psychological complications, two serious and requiring psychiatric intervention, predominantly because of poor seizure control. Clearly, there may have been confounding factors, including their pre-morbid mental health status and the adverse effects of medication, and specifically, topiramate. Seizures may affect relationships, self-esteem, continuing education, career opportunities and driving which in turn may limit social functioning, stigma and quality of life [10]. Such factors must be carefully considered in the discussion of all available treatment options with young people and their families.

4.2. Towards individualised care

Treatment options should always be tailored to a patient's circumstances and priorities. There should be an open and realistic discussion about treatment alternatives that should include a balanced discussion of relative risks and benefits. Such discussions may need to occur at the time of diagnosis, particularly in girls of childbearing age. Whilst this might be considered a statement of the obvious, this approach is not always followed in clinical practice as demonstrated in all six of our cases where there was no documented discussion on treatment choices. It may also be difficult to provide a balanced discussion without prejudicial bias by the clinician. An over-liberal use of valproate might result in increased foetal exposure to valproate with consequent malformations and cognitive delay. Conversely, overly restricted use of valproate might result in unnecessary seizures and associated consequences.

Decisions made by patients are heavily dependent upon the information provided by clinicians. If the clinicians' interpretation of current evidence is that preventing teratogenicity is the priority, the risk of teratogenicity might be emphasised in any discussion and valproate might not even be offered as a treatment option.

Decisions made in clinic consultations might be helped by better evidence about the priorities and preferences of young people with epilepsy although there is a currently a dearth of such evidence.