Sultiame revisited: treatment of refractory absence seizures

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ABSTRACT – Sultiame is recommended for the treatment of benign epilepsy of childhood with centrotemporal spikes, electrical status epilepticus during slow-wave sleep, as well as other genetic (idiopathic) focal epilepsies. Sultiame is not traditionally considered a treatment choice for idiopathic generalised epilepsy, and it does not appear on the list of drugs recommended for treatment of absence seizures. We report the efficacy of sultiame in treating three children with drug-resistant absence seizures and discuss the potential use of sultiame beyond the idiopathic focal epilepsies.

Key words: sulthiame, absence seizure, refractory, idiopathic focal epilepsy, childhood absence epilepsy

Sultiame is a sulfonamide derivative and central carbonic anhydrase inhibitor (Wirth et al., 1960), which has been used for over 50 years for the treatment of epilepsy. It was introduced in the 1960s as adjuvant treatment for focal epilepsies (Garland and Summer, 1964). Its popularity waned the following decade due to concerns about its safety and efficacy as an antiepileptic drug (AED). Sultiame is used largely in central Europe (Germany, Switzerland, and Austria) and Israel for idiopathic focal epilepsies (IFE), benign epilepsy of childhood with centrotemporal spikes (BECTS), juvenile myoclonic epilepsy (JME), and electrical status epilepticus during slow-wave sleep (ESES) (Ben-Zeev et al., 2004; Fejerman et al., 2012). The drug is not frequently used in Ireland or the United Kingdom, where it is not routinely prescribed for the treatment of BECTS, compared to central Europe. Sultiame is not routinely recommended for the treatment of idiopathic generalised epilepsies (IGE), including absence seizures (Vrielynck, 2013). Herein, we describe the efficacy of sultiame in the treatment of drug-resistant absence seizures in the setting of presumed idiopathic or genetically influenced generalised epilepsy in three paediatric patients refractory to multiple AEDs, as well as the ketogenic diet and steroids. With the introduction of sultiame, there was significant reduction of absence seizures with no adverse side effects. This report highlights the potential benefit of sultiame for the treatment of refractory absence seizures and its potential use beyond IFE in children.
Case study

Patient 1

A 13-year-old girl presented at the age of six with absence seizures (abrupt behavioural arrest, upward eye deviation, and oral automatisms, with 50 witnessed events per day). EEGs showed frequent absence seizures (duration: 5-20 seconds) with generalised regular 3-Hz spike-wave discharge and no interictal discharges (figure 1). With the onset of absence seizures, school performance declined. Significant seizure improvement was never achieved despite optimal dosing regimens and combinations of ethosuximide, topiramate, lamotrigine, sodium valproate, zonisamide, clobazam, amantadine, carbamazepine, stiripentol, and steroids. She commenced the ketogenic diet aged 8 years, with an initial improvement, but efficacy waned and seizure frequency returned to baseline. In addition, while on the ketogenic diet for 22 months, she developed infrequent generalised tonic-clonic (GTC) seizures aged 10 years. Sultiame was introduced at 12 years, in addition to pre-existing zonisamide. Now, at a dose of 300 mg/day (10 mg/kg/day), there is significant reduction in absence seizures (0-5 per day), but no difference in frequency of GTC seizures (one per month). There is substantial improvement in her concentration and school performance.

Patient 2

A 12-year-old boy presented at the age of 3 to a peripheral hospital with daily episodes of unresponsiveness, infrequently associated with lip smacking and urinary incontinence. At 5 years, he presented to us with frequent absence seizures (abrupt brief [<10 seconds] impairment of consciousness with lip smacking, with up to 20 seizures per hour). Developmental milestones were normal. His older sister was diagnosed with typical childhood absence epilepsy (CAE) aged 7 and was seizure-free with ethosuximide. EEGs showed generalised regular spike-wave activity at 3-3.5 Hz during absence seizures. Interictal EEG showed bursts of generalised spike-wave, polyspike and polyspike-slow-wave discharges. Treatment with multiple AEDs failed to achieve seizure control (ethosuximide, sodium valproate, levetiracetam, clobazam, lamotrigine, and topiramate). At 10 years, sultiame was added to the pre-existing sodium valproate and clobazam. At a dose of 125 mg/day (2.5 mg/kg/day), he became seizure-free and has remained seizure-free (for two years). Clobazam was stopped and he was weaned off sodium valproate. Repeat EEG (figure 2) has improved with minimal interictal spike-wave activity and no absence seizures, even with hyperventilation.

Patient 3

A 10-year-old girl presented at the age of 3 with absence seizures (unresponsiveness with upward eye deviation, lasting for up to 15 seconds), which were observed clinically, 60-100 times a day. Prior to presentation, she had a single febrile convulsion at two years and motor delay (walked at 30 months). With the onset of frequent seizures, her gait had become unsteady, but with no cerebellar signs. EEGs demonstrated frequent absence seizures (lasting for 7-15 seconds) with 3-Hz generalised regular spike-wave discharges (figure 3). Interictal EEG showed brief generalised

Figure 1. EEG during an absence seizure showing generalised regular 3-Hz spike-wave activity. Sensitivity at 20 µV/mm to allow better visualisation of the spike-wave pattern.
Sultiame and refractory absence seizures

Figure 2. Follow-up EEG after adding sultiame. Infrequent generalised spike/polyspike-wave activity, but no absence seizures (even with hyperventilation).

Figure 3. EEG during an absence seizure showing 3-Hz generalised regular spike-wave activity. Sensitivity at 30 μV/mm to allow better visualisation of the spike-wave pattern.

spike-and-slow-wave discharges, shorter in duration (≈1 second). Treatment with multiple AEDs, including sodium valproate, ethosuximide, lamotrigine, zonisamide, and levetiracetam, failed to achieve any meaningful seizure control. Mild learning disability was documented based on neuropsychological assessments. With the introduction of pulsed intravenous methylprednisolone, there was complete resolution of seizures, associated with an improvement in balance and cognition. Treatment continued with daily, then alternate day, oral steroids, with an initial four-month seizure-free period. Weaning oral steroids to twice weekly dosing was not tolerated, with increased frequency of absence seizures (up to 100 per day). Increasing oral steroids once again to daily dose had some response, but not as profound as before. Ongoing daily absence seizures continued. Sultiame was commenced at 8 years of age with clobazam and steroids, with marked and sustained improvement in seizure frequency. Oral steroids were tapered slowly and stopped. She is now two years seizure-free on a dose of sultiame 300 mg/day (7 mg/kg/day). Improved seizure control was associated with improvement in balance and cognition. The most recent EEG showed no interictal discharges and no absence seizures, even with hyperventilation.
Table 1. Practical guideline for Sultiame dosing and use in children

| Dosage          | Start dose 3 mg/kg/day  
| Dose increased by 25-50 mg OD weekly  
| Aim 10-15 mg/kg/day  
| Maximum Dose: 600 mg/day  |
| Side Effects    | Hyperpnoea, paraesthesia, cognitive impairment, anorexia, nausea, dizziness  |
| Monitoring      | No drug level monitoring  |
| Drug Interaction| Phenytoin and lamotrigine  
| Can increase levels, need to monitor more frequently at start |

GLUT-1 transporter deficiency was ruled out chemically in all, and genetically in Patients 1 and 3.

Discussion

Our patients had absence seizures with typical clinical accompaniments (automatisms and occasional eye rolling) and always exhibited clear EEG correlation of 3-3.5-Hz regular generalised spike-wave discharges. The presence of interictal epileptiform abnormalities and the resistance of absence seizures to multiple AED regimes exclude clearly defined typical CAE as the underlying epilepsy syndrome. The clinical presentation of the patients did not fit completely with any of the other specific ILAE-defined absence epilepsy syndromes such as juvenile absence epilepsy (JAE) or JME (Berg et al., 2010). However, the absence seizures themselves are consistent with typical absence seizures; brief, with EEG correlation of regular generalised 3-Hz spike-wave discharges. We emphasise that the seizures themselves are not what are known as “atypical absence seizures” (which typically occur in association with other types of seizures, in the setting of intellectual impairment and/or exhibit ictal EEG with slower and less regular generalised spike-wave complexes at <2.5 Hz). There were no focal features clinically or electrographically. Both clinical and EEG features are probably consistent with genetically influenced generalised epilepsy (formerly known as IGE) that does not fit completely with the very well defined CAE, JAE or JME.

Recommended first-line AEDs for the treatment of typical absence seizures include ethosuximide and sodium valproate (Vrielynck, 2013). Berg and colleagues (Berg et al., 2014) favoured ethosuximide as first-line treatment rather than sodium valproate due to reported better long-term outcomes. Second-line medications include clobazam, clonazepam, lamotrigine, levetiracetam, topiramate, and zonisamide (Vrielynck, 2013) combinations of the above medications such as lamotrigine and valproate are often used. Sultiame is not routinely recommended for the treatment of absence seizures (Vrielynck, 2013). On review of the literature, we identified two historical reports discussing the use of sultiame as adjuvant therapy in a subgroup of patients with absence seizures in the setting of generalised epilepsy (Gayral et al., 1965; Lerman and Nussbaum, 1975). Recognised dose-related side effects of sultiame include hyperpnoea, paraesthesia, cognitive impairment, and anorexia (Garland and Summer, 1964). In our patients, we used doses up to 10 mg/kg/day and did not observe any side effects (table 1). A dose of 5 mg/kg is found to be well tolerated for the treatment of BECTS, with good seizure control (Ben-Zeev et al., 2004).

The mechanism of action of sultiame in epilepsy is not fully understood; it may involve inhibition of intracellular carbonic anhydrase and/or voltage-gated sodium channel blockade (Madeja et al., 2001). Siniatchkin and colleagues demonstrated that a single dose of sultiame increased the resting motor threshold. They postulated the inhibition of carbonic anhydrase, lowered intracellular pH, and reduced conductivity of voltage-operated sodium channels to be the likely antiepileptic mechanism, mirroring the findings of Madeja and Wolf (Siniatchkin et al., 2006). The efficacy of sultiame in treating absence seizures in our patients (in addition to its previous success in the treatment of IFE, BFEC, ESES) led us to hypothesise that its efficacy is related to the underlying mechanism of a likely genetic epilepsy, as opposed to being specific to focal epilepsy. The benefit of sultiame in the treatment of ESES tempted us to extrapolate its efficacy to absence seizures, given the underlying likely genetic influence driving the conventional regular EEG spike-wave activity. Mutations in GABA_A and GABA_B receptors have been identified, not only in patients with absence epilepsy, but also in those with spike-wave discharges (Siniatchkin et al., 2006). In animal studies, acetazolamide, a more potent carbonic anhydrase inhibitor, reduces the HCO_3 gradient activity, blocking the GABA repolarizing response (Siniatchkin et al., 2006). One can hypothesise that sultiame acts...
Sultiame and refractory absence seizures in a similar manner in the genetically influenced epilepsies, regardless of their focal or generalised EEG signature or clinical classification.

**Conclusion**

Sultiame should be considered for the treatment of refractory absence seizures. Given the relatively mild side effects of sultiame, there is a strong case for its use over other options, such as steroids which have significant side effects. It is perhaps time to revisit sultiame and consider it as a broader spectrum AED, to be used as third/fourth-line treatment for the genetically influenced epilepsies (both focal and generalised). We acknowledge that the small patient number (given the rarity of this degree of refractoriness of absence epilepsy in one institution) is a relative weakness. Thus, further reports of sultiame use in refractory absence seizures, and indeed further investigation into its mechanism of action, should help strengthen and confirm our finding.

**Supplementary data.**

Summary didactic slides are available on the www.epilepticdisorders.com website.

**Disclosures.**

None of the authors have any conflict of interest to disclose.

**References**


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**TEST YOURSELF**

(1) What are the clinical and EEG features which distinguish between typical and atypical absence seizures?

(2) What types of seizures and/or epilepsy syndromes should treatment with sultiame be considered for?

(3) What are the potential side effects of sultiame?

*Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section “The EpiCentre”.*