Stiripentol use in adults with Dravet Syndrome

Purpose of document

To clarify the position of stiripentol (STP) as an antiepileptic drug (AED) for the treatment of drug-resistant generalised tonic-clonic seizures in Dravet Syndrome (DS).

Statement

*STP initiated in childhood and proving effective for seizure control can and should continue to be prescribed into adulthood for as long as this is effective, as this is within the current marketing authorisation. Confusion may arise from the BNF entry for STP which currently notes it is licensed for use in children aged 3-17: in some cases, this has led to problems with its continued provision for children transitioning to adult care at 17. This document is intended to assist neurologists in ensuring continued provision of STP in this situation. The BNF has now agreed to clarify its entry on STP.*

*STP does not have a UK marketing authorisation for initiation in patients >18 years of age. Hence at present for people with DS above this age, it may be only initiated off-label, outside the terms of its licence.*

Background

Dravet Syndrome (DS) is a severe genetic epileptic encephalopathy with onset in infancy, often associated with drug-resistant epilepsy, developmental slowing, cognitive impairment, occurrence of status epilepticus and elevated risk of early mortality\(^1\)\(^2\). In at least 85% of cases, the cause is a mutation in the voltage-gated sodium channel type I alpha subunit gene, *SCN1A*. The main challenges include seizure control, prevention of status epilepticus and optimizing development of cognitive function, where possible. Additional comorbidities often present in adulthood including dysphagia, cerebellar symptoms and gait disturbances, and most adults with DS cannot live independently\(^3\)\(^4\).

Stirpentol (STP) is an AED which was licensed under the European Medicine Agency Orphan Drug scheme in 2001. It has been approved in Europe, Japan, and Canada, as adjunctive therapy for refractory generalized tonic-clonic seizures in children with DS whose seizures are not adequately controlled with clobazam and valproate alone (there are no data from randomised controlled trials on clobazam in association with valproate in DS). Until recently, STP was the only treatment for which a phase 3 randomized, placebo-controlled, clinical trial had been performed in patients with DS\(^5\). This included 41 children with DS who had placebo (n=20) or STP (n=21) added to valproate and clobazam during a double-blind period of two months, after a baseline period of one month. In the STP group, 15 (71%) children were responders (defined as having at least a 50% reduction in the frequency of clonic or tonic-clonic seizures) on STP (including nine free of clonic or tonic-clonic seizures), whereas only one (5%) was a responder on placebo (none were seizure-free).

STP is recommended by NICE CG 137 in DS:

"Adjunctive treatment in children, young people and adults with Dravet syndrome"
1.9.9.3 Discuss with a tertiary epilepsy specialist if first-line treatments (see recommendation 1.9.9.2) in children, young people and adults with Dravet syndrome are ineffective or not tolerated, and consider clobazam or STP as adjunctive treatment. [new 2012]’

DS carries a huge financial burden. The substantial cost drivers include hospitalisations and in-home medical care visits: these were estimated at $11,565 per year and $9,894 per year respectively in a recent survey (Whittington et al, 2018). Achieving seizure freedom in DS would be expected to reduce the costs associated with uncontrolled seizures (e.g., admissions to hospitals) and improve quality of life measures. The recommended dose of STP is up to 50 mg/kg/day. The estimated daily drug cost for an adult weighing 70 kg would be £57.52, or £20,994 per year6. A retrospective evaluation of health-care utilization over a 2-year period included 13 patients with DS at an outpatient clinic of a German epilepsy centre. Of these, nine (mean age 10.3, range 3–23) were switched to adjunctive treatment with STP and clobazam and experienced more than 25% reduction in seizure frequency between baseline and follow-up phases of 1 year each7. When effective, continuing STP in adulthood is likely to reduce the economic burden of DS.

DS is increasingly recognized and newly diagnosed in adulthood, and many children with DS survive to adulthood. The underlying disease, and the causal genetic mutation, of course do not change on transition to adulthood. Children with DS often enter adolescence and adulthood with STP as part of their medication regime. There are now a number of studies showing that the efficacy and safety of STP are maintained in adult patients8-12. We previously conducted an observational clinical audit in our epilepsy service at the National Hospital for Neurology and Neurosurgery, UCLH, London, to document the effectiveness and tolerability of STP in a cohort of 13 adults with DS. We found a responder (defined as more than 50% reduction in all seizure types) rate of 23% at 36 months, a retention rate of 62% after 1 year and 31% after 5 years. In 23% cases there were side effects leading to STP withdrawal, but overall we found a good tolerability profile11. A larger study of 40 adult patients with DS recently confirmed that the efficacy and safety of STP, in association with valproate and clobazam, are maintained in the very long term (up to 24 years of exposure) during adulthood12. When STP had been started in childhood, and continued into adulthood, 25% of people with DS exhibited >1-year seizure-free periods during adulthood and none had status epilepticus after 25 years of age. The authors also suggest that prolonged treatment with STP tends to positively impact the late prognosis of the epilepsy, especially when initiated before adolescence12.

Difficulties have been reported in continuing prescription of STP when children with DS, on STP, pass their 17th birthday. This can increase anxiety for children with DS and their affected parents, and at worst could lead to deterioration in seizure control if STP prescription were interrupted. Some current disparities in public documents on STP may lead to confusion.

The BNF/BNFc entry could be confusing, as the BNFc specifically mentions children (unlike the marketing authorisation):

The BNFc indicates:

“Indications and dose

Adjunctive therapy of refractory generalised tonic-clonic seizures in children with severe myoclonic epilepsy in infancy (Dravet Syndrome) in combination with clobazam and valproate (under expert supervision)
ABN Epilepsy Advisory Group: Stiripentol use in adults with Dravet Syndrome  March 2019

By mouth

- For Child 3–17 years

Initially 10 mg/kg daily in 2–3 divided doses, increased to up to 50 mg/kg daily in 2–3 divided doses, titrated over minimum of 3 days.”

STP is not included in the main BNF (as it is not something that would be initiated in adulthood according to the marketing authorisation, but could be continued into adulthood).

The BNF have already agreed to adjust their STP entry.

The summary of product characteristics (SmPC) for STP is held on the EMA site and states: “Therapeutic indications. Diacomit is indicated for use in conjunction with clobazam and valproate as adjunctive therapy of refractory generalized tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy (SMEI, Dravet’s syndrome) whose seizures are not adequately controlled with clobazam and valproate”, and later in the SmPC: “Patients aged ≥ 18 years of age. Long-term data has not been collected in a sufficient number of adults to confirm maintenance of effect in this population. Treatment should be continued for as long as efficacy is observed.”

Therefore STP initiated in childhood and proving effective can and should continue to be prescribed into adulthood, as this is within the marketing authorisation. However, STP does not have a UK marketing authorisation for initiation in patients >18 years of age. Hence at present it may be only initiated off-label, outside the terms of its licence. As explained by the MHRA in a drug safety update, the prescriber should follow relevant professional guidance, taking full responsibility for the decision; informed consent should be obtained and documented. In terms of an extension of the marketing authorisation, the company would have to apply to the EMA with new data showing efficacy in this group of patients (i.e. people with DS for whom STP had been initiated after the age of 18).

National funding decisions have been made in Scotland and Wales, but not in England or Northern Ireland:

National funding/access decisions

Scottish Medicines Consortium (SMC) Decisions

“The Scottish Medicines Consortium has advised (September 2017) that stiripentol (Diacomit®) is accepted for use within NHS Scotland in conjunction with clobazam and valproate as adjunctive therapy of refractory generalised tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy whose seizures are not adequately controlled with clobazam and valproate.”

All Wales Medicines Strategy Group (AWMSG) Decisions

“The All Wales Medicines Strategy Group has advised (November 2017) that stiripentol (Diacomit®) is recommended for use within NHS Wales for use in conjunction with clobazam and valproate as adjunctive therapy of refractory generalized tonic-clonic
seizures in patients with severe myoclonic epilepsy in infancy (SMEI, Dravet syndrome) whose seizures are not adequately controlled with clobazam and valproate.”

Many adults with DS continue to experience generalised tonic-clonic seizures that pose an ongoing threat to their life, with a high mortality rate. Most patients with DS have a mutation in the SCN1A gene whose pathophysiological effect cannot be reversed. STP can and should therefore be continued in adulthood when initiated in childhood for as long as efficacy is observed, without any upper age limit: this is in keeping with the marketing authorisation.

Given the effectiveness demonstrated in previous studies and its reasonable tolerability profile, STP could be initiated in adults with DS and drug-resistant epilepsy when first-line treatments are ineffective or not tolerated, in keeping with recommendations from National Institute for Health and Care Excellence guidelines in the UK, but this would require an Individual Funding Request and would be considered off-licence prescription.

Issues may arise due to lack of awareness of what the SmPC actually states, not helped by the fact that it is not held by MHRA or at eMC (both commonly used to access SmPC information in the UK). However, a CCG medicines optimisation/management team should be aware of the EMA site, how to access SmPCs, and their importance as legal documents. This document has been produced to provide guidance and information for neurologists faced with difficulties in use of STP in DS.

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References


16. https://www.scottishmedicines.org.uk/SMC_Advice/Advice/524_08_stiripentol__DIACOMIT_/stiripentol_Diacomit

17. www.awmsg.org/awmsgonline/app/appraisalinfo/3468
