Successful treatment of super-refractory tonic status epilepticus with rufinamide: first clinical report

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Introduction

Rufinamide (RUF) is a novel antiepileptic agent that has entered clinical use within the last 10 years, thought to act through modulation of sodium channel activity[1].

Based on evidence from several independent randomised controlled trials (RCTs), RUF is used as an adjunctive agent in the treatment of Lennox-Gastaut syndrome (LGS)[2]. LGS is an epileptic encephalopathy syndrome, typically with onset in childhood, characterised by the presence of multiple seizure types including tonic, atonic and atypical absence seizures, and electroencephalography (EEG) showing slow spike-waves during waking, and fast rhythmic activity during sleep, as well as psychomotor delay and personality disorders.

In addition to its use in LGS, RUF has shown some efficacy in other refractory epilepsy syndromes in both children and adults[3], though retention rates appear highest in LGS[4].

We are not aware of any prior experience of the use of RUF in status epilepticus. Here we present a case in which RUF was used as an adjunctive agent to treat super-refractory tonic status epilepticus, in a young adult male with an unusual epilepsy syndrome sharing some features with LGS.

Case Study

A 24-year old man with mild autistic spectrum disorder and learning disability presented with a recurrence of tonic seizures. He had previously had similar seizures at the age of 7, which came under rapid control on carbamazepine and valproate. These were withdrawn at the age of 10, and since then he had been seizure free without treatment.

Seizures consisted of sudden tonic abduction and extension of the arms into a "crucifix" posture associated with loss of awareness, lasting between 3 and 10 seconds, followed by very rapid recovery of awareness. Within days of recurrence, with no identified precipitant, the seizures rapidly escalated until they were occurring every 1-2 minutes, more than 95% of the time. He was admitted initially to a neurology ward, and after 2 weeks with little progress to a neurological intensive care unit. Magnetic resonance brain imaging showed no structural abnormality, cerebrospinal fluid results were unremarkable and cytogenetics showed no chromosomal abnormality. Antineuronal antibody screening was also subsequently confirmed as negative.

Benzodiazepines, phenobarbitone and levetiracetam had no impact. Valproate was partially successful at high doses (up to 4.8g/day), but led to a hyperammonaemic encephalopathy. Burst suppression was eventually achieved only with a combination of ketamine, propofol and barbiturate with hypothermia. Subsequent trials with high doses of topiramate, lacosamide, phenobarbitone and further benzodiazepines were of no benefit, with seizure recurrence on multiple attempts at withdrawal of anaesthetic agents over a 4 week period.

As the electro-clinical picture included features reminiscent of LGS (Figure 1), after informed discussion with the patient's family, RUF was rapidly titrated up to a total dose of 3g/day over 10 days. Seizures abated completely for several days despite withdrawal of all sedation, with no apparent adverse effects. There were no significant changes in clinical observations, haematinics or biochemistry beyond improvements in his seizure frequency and responsiveness over this period.

Intermittent seizures and self-limiting clusters subsequently recurred, but further improved on RUF at 4.4g/day, in combination with higher dose Valproate. Clobazam was of no clear benefit, but additional carbamazepine, started on the basis of the good response reported in childhood was associated with further reductions in seizure frequency. The ketogenic diet was also trialled in hospital with some benefit, but not maintained or tolerated in the longer term. He was discharged home after 3 months in hospital with no neurological sequelae, though not yet seizure free. At last follow up (18 months later) he was stable and having brief tonic seizures approximately monthly, on a combination of Rufinamide, Valproate, Carbamazepine together with low dose phenobarbitone and clobazam which were being slowly withdrawn.

Discussion

Rufinamide is a relatively new anti-epileptic agent, which is currently licensed specifically and only for adjunctive treatment in patients with LGS. Preclinical evidence suggests that it is likely to have a broad spectrum of action[1] and there is some evidence of its efficacy in other clinical contexts[6], so it may well be possible for its range of uses in clinical practice to expand in the future.

Here we have presented an unusual clinical case in which there was a very dramatic recurrence of frequent tonic seizures in a young man following many years of seizure-freedom, leading rapidly to highly refractory tonic status epilepticus. The rapid introduction of RUF, in combination with other treatments as described, was successful in controlling the seizures and allowing sedation and anaesthetic agents to be withdrawn.

In adults, initiation of RUF is recommended in 200mg increments no faster than every 2 days, up to a maximum doses of 3.2g/day. Neither the manufacturers nor several international experts contacted for advice (personal communication, Dr Cock) had any information on more rapid escalation nor RUF use in status epilepticus. RUF was started at 400mg and escalated to 3g/day over 10 days, approximately double the recommended rate with good effect and without complications. Encouraged by a partial response at 3g/day, despite withdrawal of anaesthesia, the dose was further escalated again without difficulties to 4.4g/day despite this being in combination with high dose Valproate (though this was later lowered).

We suggest that RUF may have a useful role in the treatment of tonic status epilepticus, and at least in our case was safely escalated at higher than recommended rates without

complications. We would encourage others to report their experience of its use in similar clinical contexts.

References

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Figure 1

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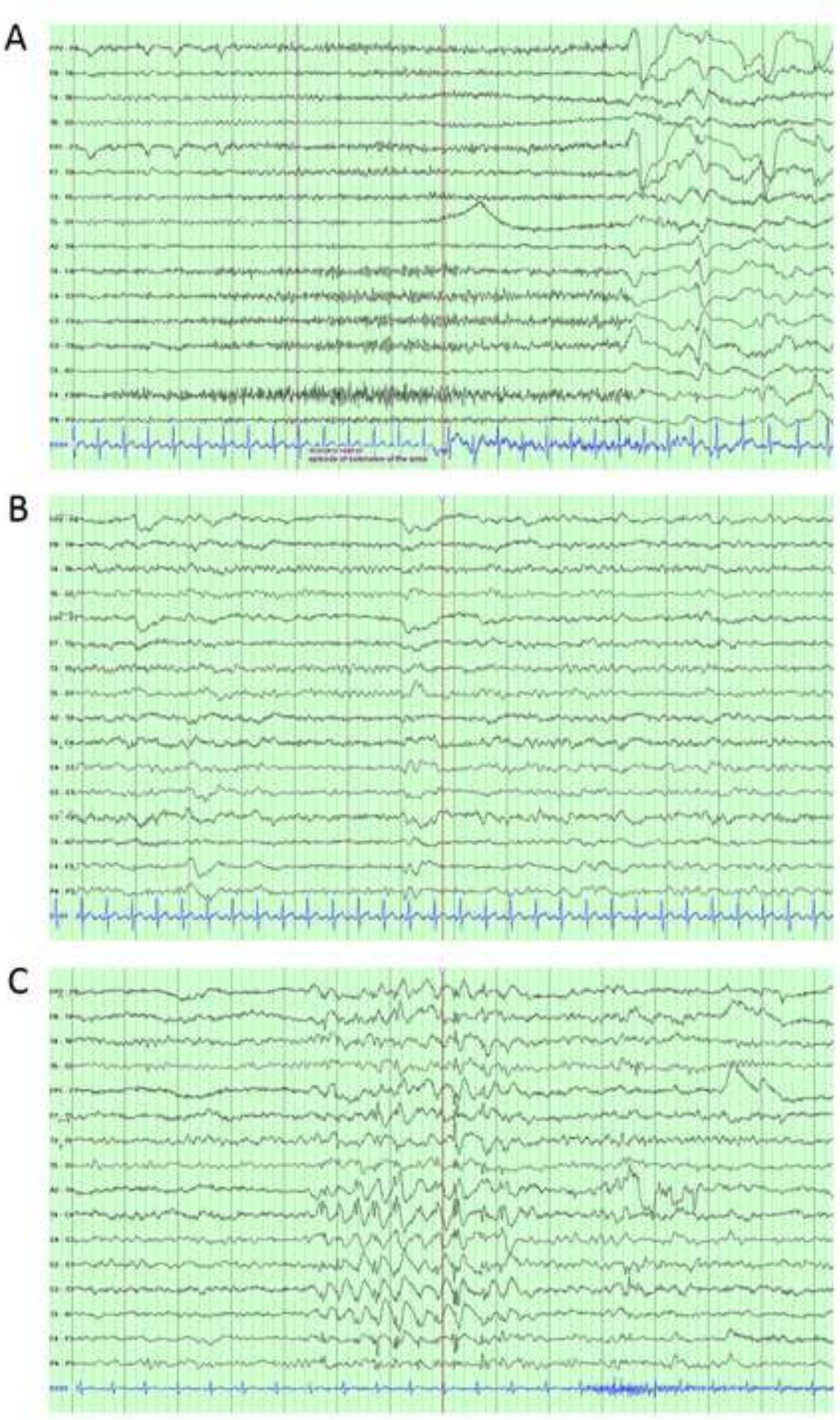

Figure 2

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