Intolerance to quinidine in a n-of-1 trial for KCNT1 associated epilepsy of infancy with migrating focal seizures

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A B S T R A C T

Quinidine has been proposed as a repurposed licensed drug for the treatment of seizures in KCNT1 gain-of-function associated Epilepsy of Infancy with Migrating Focal Seizures (EIMFS). Sparse evidence from case reports suggests limited effectiveness and tolerability. Here we report the adaptation of a n-of-1 trial protocol and results of adjunctive quinidine intervention. We adapted a n-of-1 trial protocol from two unpublished protocols and with expert advice including input from pediatric neurology, cardiology and pharmacy colleagues. We tailored this protocol to a severely disabled patient with EIMFS and a de novo c.1420C>T p.Arg474Lys missense variant. We discussed outcome measures with the family of the patient and initiated adjunctive inpatient quinidine treatment with appropriate safety measures. The trial was terminated as a result of intolerable gastrointestinal adverse effects following the initiation dose. Subsequent reports suggest that quinidine may not be effective for this genotype. Quinidine is poorly tolerated across cardiological and neurological indications. Current pooled evidence suggests limited effectiveness for KCNT1 associated epilepsies at doses <40mg/kg/d. It is important to report all clinical evidence in precision medicine trials, whether positive or negative, to counter publication bias. This study highlights universal issues around outcome measurement and the evaluation of evidence in rare disease interventions.

1. Introduction

Pathogenic variants in KCNT1, a gene encoding for a sodium-related potassium channel, are the leading known cause of the rare and severe syndrome of epilepsy of infancy with migrating focal seizures (EIMFS) (1). EIMFS is an early epileptic encephalopathy, with onset in the first 6 months of age, characterized by heterogeneous focal seizures, which appear to migrate through different brain regions or hemispheres, even in the same epileptic episode [1]. Patients affected by EIMFS are usually resistant to therapy with conventional antiseizure medication (ASM) and often extremely disabled due to associated neurological impairments of movement and communication. Therefore new therapies including repurposed drugs such as quinidine [3] and novel therapies like antisense oligonucleotides [3] offer prospects of improvement over existing ASMs.

Quinidine is an anti-arrhythmic agent, which has been used for cardiac arrhythmias for over a century [4], although it was largely abandoned because of pro-arrhythmic effects causing QT prolongation and Torsades des Pointes. Its pleiotropic pharmacological effects are expressed on sodium, calcium and potassium channels [5] In particular, it is a partial-antagonist of the KCNT1 channel [6]. The pathogenic mechanism of KCNT1 mutation is not fully understood, but it seems that a gain of function of the potassium channels in excitatory neurons may lead to a more rapid repolarization (ie shortened action potentials) and a higher firing rate of neurons [6]. Most missense mutations in KCNT1 causing epilepsy show a “gain-of-function” effect, so that the ionic currents are increased [6]. Experimental models in neuronal cells demonstrate that quinidine can reverse the enhancement of KCNT1 currents caused by gain-of-function mutations [6,7]. Quinidine has therefore been used as a proposed precision medicine in a handful of KCNT1 mutation patients with mixed results, summarised recently [2,8–12].

The history of precision medicine in monogenic epilepsies is short [13] and remains largely in the formative anecdotal stage of case
reports, small case series and n-of-1 trials. A more formal structure for evaluating proposed precision therapies is gradually emerging. Challenges to collecting comparative effectiveness evidence for rare diseases via international collaboration include the absence of consensus for investigation protocols, outcome measures and case selection. Published protocols for n-of-1 trials generally lack the rigour and detail of large randomised controlled trials and consequently require adaptation for local implementation.

Here we report the adaptation of a protocol for adjunctive quinidine treatment in a patient with EIMFS and KCNT1 pathogenic predicted gain-of-function variant and the results of a n-of-1 trial. Our aims were (i) adapt a n-of-1 protocol for use at Evelina London Children’s Hospital, UK; (ii) agree appropriate outcome measures with the patient’s family; (iii) evaluate effectiveness and tolerability of adjunctive quinidine.

2. Methods

2.1. Protocol adaptation

We used the Children’s Hospital of Philadelphia (CHOP) and Munich protocols as our starting point [2,12] and sought additional guidance on dosage and response from experienced colleagues (Dr David Bearden, Boston 14th September 2017; Dr Steffen Leiz, Munich, 26th June 2017 personal communications) and through search of the extant literature in EMBASE and PubMed in January 2018 [6–10]. The CHOP protocol used final doses of 40–150mg/kg/d for EIMFS [2] and responses were seen when blood level was maintained between 2-5mg/l; in Munich the total dose used was 40mg/kg/d. Quinidine was administered orally every 6 hours in both protocols. In the initial phase the dose was 2-10 mg/kg/day, rising to 40-60 mg/kg/day. Time to response was reportedly slow, with a minimum of two weeks at maintenance dose before a change in seizure frequency was observed. At the time of protocol development, significant improvement in seizures and alertness had been seen in 50% of (n=15) patients: four patients had sustained seizure freedom, four had about a 50% reduction in seizures, and seven had either minimal response or stopped due to adverse effects. Results seemed to be better in younger children with the EIMFS phenotype. Although QTc prolongation had been observed, there were no significant arrhythmias; a small quinidine trial for KCNT1 pathogenic variants in sleep-related hypermotor epilepsy was limited by lack of efficacy and prolonged QT interval [14]. We discussed drafts of the protocol with colleagues in cardiology and pharmacy (see acknowledgements). Specific points for adaptation towards this patient included the pre-intervention baseline observation period; the screening tests to be checked at baseline; cardiac monitoring schedule; dosing and the dosage escalation schedule. The final protocol procedures are summarised in Table 1.

2.2. Study design

A prospective, unblinded, observational study based at the Department of Paediatric Neuroscience, Evelina London Children’s Hospital, London, UK in June 2018. A three-month baseline observation period without adjunctive treatment or changes to medication to be followed by a six-month period with adjunctive Quinidine.

2.2.1. Inclusion criteria

1. Individual affected by EIMFS and drug resistance defined as absence of seizure remission with ≥2 AEDs
2. At least one seizure per day for at least five days a month over a period of three months prior to enrolment.
3. Confirmed pathogenic gain-of-function variant in KCNT1 gene.
4. Dosage of ASMs stable for at least 4 weeks before enrolment.

Table 1

| Schedule of procedures for n-of-1 quinidine trial for KCNT1 gain of function associated EIMFSs. |
|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|
| Pretrial and Initiation Phase | Dose escalation Phase |
| Timepoint | T0: 3 mo Pre-Trial | T1A Test and Initiation doses | T1B: 48-72 hrs after initiation dose | Escalation |
| Terminology | Seizure diary | Seizure diary | Seizure diary | Seizure diary |
| Procedures | Renal Function | Renal Function | Renal Function | Renal Function |
| Blood tests | Acid Base | Acid Base | Acid Base | Acid Base |
| | Liver Function | Liver Function | Liver Function | Liver Function |
| | Full Blood Count | Full Blood Count | Full Blood Count | Full Blood Count |
| | 90 min outpatient EEG | 90 min outpatient EEG | 12 lead | 12 lead |
| | 12 lead | 12 lead | ECG [15] after test | ECG [15] after test |
| | after test done | after test done | done | done |
| | 12 lead | 12 lead | ECG [1] after initial dose | ECG [1] after initial dose |
| | ECG [1] before discharge | ECG [1] before discharge | 12 lead | 12 lead |
| | ECG [2] before discharge | ECG [2] before discharge | ECG [2] before discharge | ECG [2] before discharge |

2.2.2. Exclusion criteria

1. Any cardiac arrhythmia on electrocardiograph within six months before intervention.
2. Previous adverse response to quinidine or similar compounds

2.3. Personalised outcome measures

2.3.1. Patient

The patient was female and had an uncomplicated delivery at term weighing 3.0 kg. Seizures emerged on day two treated with Phenobarbitone, then Pyridoxine and Phenytoin. No initial focal or other neurological deficits were noted, head circumference was normal at 36cm and there was no organomegaly. A neurometabolic screen showed no persisting abnormalities, brain imaging and ophthalmology assessment were normal. Early descriptions supported multifocal seizures. However, by nine weeks of life the clinical picture had changed to include focal tonic spasms with or without automatisms and fearful episodes with screaming. The tonic events were accompanied by bursts of generalised EEG discharge before discharge.

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There was a temporary response to Clonazepam and Sodium Valproate and early developmental progress appeared relatively preserved; but then deteriorating seizure control in spite of trials of Carbamazepine, Prednisolone, Vigabatrin, Pyridoxal Phosphate and Topiramate. Seizures were described as absences, myoclonic seizures, epileptic spasms...
and generalised tonic-clonic seizures. By seven months her head circumference had fallen to between the 3rd and 10th centiles with marked developmental delay. An extended metabolic screen and array CGH were negative. Seizures continued to be poorly responsive to treatment including ketogenic diet. By age five her head circumference was below the 0.4th centile, she was solely gastrostomy fed and had a four-limb motor disorder with progressive neuromuscular scoliosis and hip dislocation. Gene panel testing revealed a KCNT1 c.1420C>T p. Arg474Lys missense variant [16].

Seizures persisted as asymmetric tonic epileptic spasms, ranging in frequency from 0-3 seizures per hour awake and 3 or more seizures per hour when asleep. EEGs showed slow background with superimposed focal discharges, in sleep resembling a burst suppression pattern. Treatment with lacosamide, zonisamide and lamotrigine had not significantly altered her profile but attempts to reduce medications were accompanied by worsening seizures. Her current medications were Zonisamide 150mg bd (10mg/kg/d) and Lacosamide 150mg bd (10mg/kg/d). It was on this background that a trial of quinidine was considered. There were cautions expressed that even if there was an improvement in seizure control this was unlikely to significantly alter her neurodevelopmental profile. However, parents felt that seizures were sufficiently intrusive to try non-standard therapies. She was not requiring concomitant medications as seizures were individually short. After discussion with parents, we agreed the following goals would represent success for the trial of adjunctive quinidine:

2.3.2. Primary outcome measures

1. Reduced emergency admissions

2.3.3. Secondary outcome measure

1. Reduced seizure number
2. Improvement in alertness

2.3.4. Baseline observation

After enrolment, the patient was to have a three-month pre-intervention baseline period during which caregivers were requested to keep a prospective seizure diary.

2.3.5. Pre-trial investigations, T₀

Renal and liver function tests including acid-base balance; full blood count, and a 24-hour ECG tape. The average QTc and its variability to be recorded (Table 1).

2.3.6. Initiation of treatment, T₁

The patient was to have a prolonged (1½ hours) period of EEG as an outpatient, and a 12 lead ECG before initiation. Initiation of quinidine treatment to be conducted as an inpatient. On the ward, a test dose of 1mg/kg/d was to be given under heart rate monitoring and a 12 lead ECG repeated after 30-60 minutes to assess QTc. If the test dose was tolerated without change in the QTc, then the initial dose of 10mg/kg/d in four divided doses (max 200mg/dose) could be given. The 12 lead ECG to be repeated after the initial dose. The patient should remain admitted (likely overnight) until all four doses have been given and another 12 lead ECG has been done prior to discharge recording the QTc. In case of arrhythmias, a 24-hour ECG tape should be repeated and no further doses administered. 48-72 hours after inpatient discharge, the patient should have QTc bloods taken as an outpatient, including the quinidine level (Table 1).

2.3.7. Dose escalation, T₂

Dosage may increase every 14-28 days by 10mg/kg/d to a maximum of 40mg/kg/d. At each dose increase, the patient would undergo outpatient EEG and have blood tests performed as in Table 1, and a 12 lead ECG (before, and 60 minutes after, dose increase) for QTc monitoring performed, dose escalation to stop when the QTc starts to increase. Quinidine levels to be checked before increasing dosage (turnaround is approximately 7 days) and no further increase implemented if the level exceeds 5mg/l. The dose should be adjusted to maintain blood level of 2-5mg/l as toxicity is thought to occur at >6mg/l. If tolerated, quinidine will be continued for 6 months or longer.

2.3.8. Follow up

At each admission and dose escalation record the interim use of any rescue medications, episodes of status epilepticus, and emergency room or hospital inpatient admissions. Laboratory studies for haematology, electrolytes, liver and kidney function, and blood concentration of quinidine to be done at baseline, and after the first, second and final dose escalation. Electrocardiogram to be performed before and after each dose escalation, in order to assess the QTc interval (which should always be maintained <450 ms).

2.3.9. Concomitant medications

No change to usual rescue therapy or interim care management. Patient to continue to take their regular concomitant prescription medications following review of potential interactions. The level of quinidine can be altered by concomitant drugs using the CYP450 pathway. Drug interactions include the ketogenic diet and most enzyme-inducing AEDs that will decrease quinidine levels [17]. Changes in acid-base status can have a profound effect on quinidine levels as this affects both absorption and renal clearance so if using other drugs that change acid-base status (e.g., topiramate, acetazolamide, bicarbonate supplements) follow blood levels frequently. In particular, stopping the ketogenic diet or topiramate may dramatically increase quinidine levels [18].

2.4. Withdrawal from study

Patient and family were free to change their minds and withdraw from the study at any time without it affecting their medical management.

2.5. Statistical analysis plan

This observational study was to have summary descriptive analysis only, comparing mean and median seizure number over pre and during-treatment blocks; also use of rescue medications and hospital admissions compared between observation and intervention periods.

2.6. Informed consent

2.6.1. Risks and benefits

The experimental medicine trial was approved by the Therapeutics Committee of Guys and St Thomas’ Hospital NHS Trust, London, UK six months after initial application. Quinidine was not stocked in the hospital pharmacy and special permission was sought for importation. Patients were counselled about the specific risks and benefits associated with the study and their consent to the trial was documented. These risks included a narrow therapeutic index, sensitivity to drug interactions (CYP-450), and dose-dependent increase in the QTc interval, which may place the patient at risk of dangerous cardiac arrhythmias. Common and rare adverse effects are listed at https://www.medicines.org.uk/emc/product/5866/smpc#gref. Benefits of quinidine treatment in this scenario may include reduced seizures and improvement in neurodevelopment and behaviour. Parents were very keen to try this.

3. Results

During the baseline observation period, the patient experienced on average seven days per month of seizure activity, with seizures occurring every 30-45 minutes throughout the night, plus two or three seizures during the day. She was taking levetiracetam, zonisamide and...
lacosamide, which had remained constant. 24-hour ECG tape revealed no abnormalities and routine haematological, liver and renal blood tests were normal.

On the day of inpatient admission, she had an EEG recording, and repeat EEG and routine blood tests. The test dose of quinidine was tolerated without adverse event. However, after the first definitive quinidine dose, the patient experienced profuse diarrhoea and vomiting so the trial was stopped. Owing to the severity of symptoms it was agreed that a re-challenge would not be acceptable. There was no evidence of infectious aetiology. An ECG recorded after the definitive dose showed T wave flattening but no QT prolongation. At follow-up 12 weeks after discharge, her seizure frequency was unchanged.

4. Discussion

It is a paradoxical irony that the evaluation of precision medicine in epilepsy has relied on empirical trial-and-error methods in its earliest days. Available protocols require thorough evaluation and modification prior to local implementation. In this case of a patient with EIMFS due to a KCNT1 pathogenic variant, the repurposed licensed drug quinidine was not tolerated and, by current evidence, appears to have limited efficacy and tolerability compared to early hopes.

Although quinidine had been used several times at the time of our n-of-1 trial, there was no consensus protocol, eligibility, genotypic prediction of effect or outcome measure. We carefully evaluated available protocols and expert advice and were cautious in our eventual dose and escalation procedures, ensuring that cardiac adverse effects could be rapidly detected and safely mitigated. We built in a three-month observation period to average out random variation in seizure pattern and a six-month intervention period to capture delayed or dose-dependent effects. We hope that the resulting protocol can inform future investigational studies, even though larger studies have been published. We also believe that this publication contributes to a more realistic appreciation of quinidine tolerability in this patient context. Unpublished trials lead to publication bias in favour of studies reporting better efficacy or tolerability.

We faced several difficulties that may be typical for non-formulary drugs – e.g., importation; a six-month process for Therapeutics Committee approval for single use; long turnaround time (one week) for quinidine levels. Such difficulties need to be factored into future orphan or repurposed drug trials. There were no functional studies on this patient’s particular variant so we used best available evidence to presume a gain-of-function – these deficits will eventually be solved by registry data and extensive functional studies. Last, because there is considerable phenotypic heterogeneity in monogenic epilepsies, we arrived at shared and realistic outcome measures for this severely disabled patient prior to the intervention to define relative success. This is an essential but easily overlooked issue in clinically complex epilepsy, where comorbidities or functional impact often overshadow seizure count [19]. Overall, the preparation for this trial required a considerable number of resources devoted to a single experimental intervention in one patient and mandates centralised resources if to be carried out at larger scale.

Ultimately quinidine was not tolerated because of gastrointestinal adverse effects, which occur in up to 50% of cardiac patients [5,20]. Adverse effects affecting the GI system account for more than half of reported adverse effects, which occur in up to 50% of cardiac patients [5,20]. Adverse effect data were not systematically reported in KCNT1 epilepsy trials [11,14,22]. We could not therefore adequately assess the potential effectiveness of quinidine; in other patients with KCNT1 associated sleep-related hypermotor epilepsy cardiac adverse effects limited the assessments of its effectiveness because high doses could not be used [1,4]. Nevertheless, others have subsequently studied EIMFS patients with the same KCNT1 c.1420C>T p.Arg474Lys missense variant and none showed benefit from quinidine treatment. Patients with other genotypes showed variable benefit but only 20% demonstrated a convincing benefit for seizure outcome in contrast to the 50% cited before this trial [11,22]. Without functional studies to provide a definite explanation for lack of response, we hypothesise that this variant distorts the intracellular quinidine binding site [23]. Variability in quinidine response in general might be explained by differences in age and developmental stage, duration of symptoms, phenotype, genetic background, concomitant medication, brain penetration and levels of active drug, and of course limited tolerability reduces the capacity for a comprehensive evaluation [11,24].

The balance between rigour and pragmatism is especially poignant in n-of-1 trials where resources are often not comparable to large-scale parallel group trials [25]. There are particular design features to be considered, for example the use of a placebo (“A”) alternating with active drug (“B”), sometimes alternating in a crossover design (eg ABAB), the number of periods, whether these should be randomised (eg AABA), potential of carryover effects and washout, and not least blinding to minimise observer bias. These design choices must now be seriously considered in the era of precision medicine.

Precision medicine for rare monogenic epilepsies is at a turning point. International initiatives to achieve consensus on methodology and to create centralised patient registries (e.g., https://kcnt1.epilepsy.org) will advance efforts to systematically evaluate evidence for effectiveness and tolerability. Additional resources to match genotype-phenotypes will assist in patient selection (e.g., https://epimwp.med.umich.edu). Single or pooled case reports are subject to publication bias and offer the lowest grade of clinical evidence with lack of controls or consideration of confounders. Even with controlled studies, there is a regression to the mean in subsequent studies that result in an attenuation of initial overestimated effect sizes. Hence robustly designed randomised trials with adaptation for rare disease prevalence and complex disability outcomes [26,27] need to be adopted in the field. However, the considerable effort involved in mounting n-of-1 trials may still be prohibitive for centres with limited trial management resources - interestingly, less than half of reported KCNT1 EIMFS patients have been exposed to quinidine five years after publication of the first case reports [11,22]. At the same time, the phase of repurposed drugs for KCNT1 may swiftly be overtaken by the advent of antisense oligonucleotide therapies, which have proven highly effective in preclinical studies [3]. Questions about patient selection and trial design will likely persist regardless of intervention.

Author information

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Ethics declaration

Informed consent has been obtained from all individuals included in this article in accordance with the regulations of the institution where the research was conducted.

All data included in this article have been de-identified to protect patient confidentiality. All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (World Medical Association Declaration of Helsinki 2000).

Declaration of Competing Interest

None of the authors have any actual or potential conflicts of interest associated with this work and there has been no financial support for this work that could have influenced its outcome.
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