

Oral clomethiazole treatment for paediatric non-convulsive status epilepticus

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ABSTRACT – We report a retrospective case study of the use of clomethiazole for treatment of non-convulsive status epilepticus in a patient not responding to benzodiazepines, illustrated by EEG and video. Clomethiazole can be considered as a safe oral option for management of non-convulsive status epilepticus when conventional treatment has failed. [Published with video sequences online]

Key words: non convulsive status epilepticus

Non-convulsive status epilepticus (NCSE) is defined as “a mental status change from baseline of at least 30 minutes duration associated with continuous or near continuous ictal discharges on EEG” (Alonso Singer *et al.*, 2012). It is usually recognised by a change in the behaviour of the child, manifesting as a change in motor behaviour, affect, arousal, cognitive behaviour, and memory (Livingston and Brown, 1988).

In children, NCSE can often be seen in the context of a pre-existing epilepsy syndrome, such as Lennox-Gastaut syndrome, Doose syndrome, juvenile absence epilepsy (Store *et al.*, 1995), or alternatively with an acute neurological insult in critically ill children requiring intensive care treatment without a previous epilepsy history (Abend and Dlugos, 2007; Tay *et al.*, 2006). The overall incidence of NCSE is difficult to determine in children and adults because of varied clinical

presentations. The incidence of NCSE in children after convulsive status epilepticus (CSE) has been reported to be between 16% and 27% (Tay *et al.*, 2006). The incidence is estimated to be 8% in patients with subarachnoid haemorrhage and 8% in coma (Abend and Dlugos, 2007). Ambulatory NCSE represents the subgroup of patients presenting in outpatient settings with mental status changes associated with the presence of seizures with subtle clinical manifestations (Akman, 2010). Ambulatory NCSE can present with an exacerbation of overt clinical seizures in a child with pre-existing epilepsy or as an initial manifestation of an acute neurological insult. It is often difficult to recognise, particularly in children with learning difficulties. Clinicians have adopted different management strategies for treating NCSE, including parenteral and oral preparations of conventional antiepileptic drugs (AEDs).



VIDEOS ONLINE

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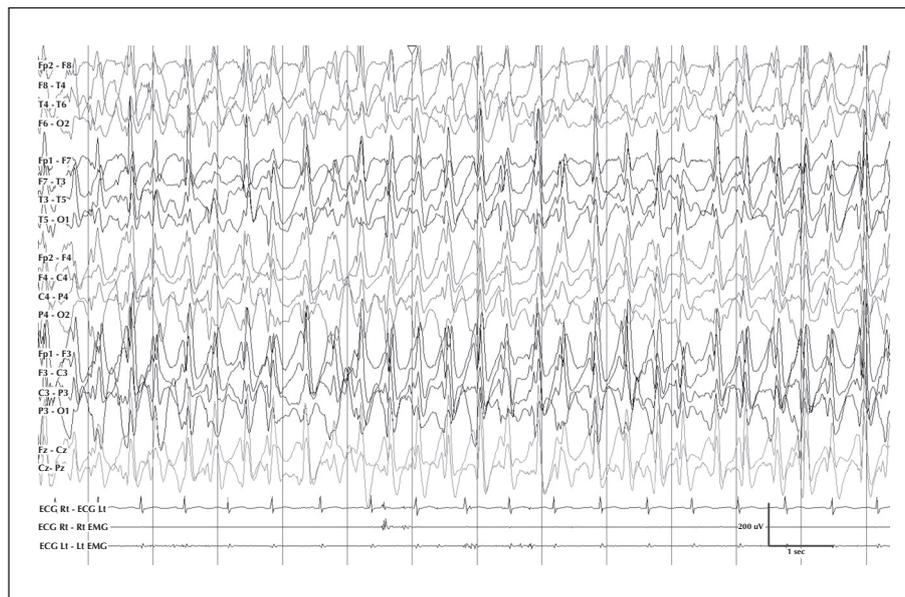


Figure 1. EEG during wakefulness, recorded after pulse oral prednisolone, at 40 mg per day, was commenced 24 hours into the cluster with no clinical improvement. This shows continuous generalised 1.5-2.5-Hz sharp/spike and slow-wave discharges.

Among the conventional AEDs, benzodiazepines are often considered the first choice. Studies have demonstrated up to 40% resistance to diazepam and midazolam when treating NCSE (Martinovic and Jovic, 1994). Here, we highlight the use of oral clomethiazole as a non-invasive, safe and effective option for treating NCSE, and review the literature.

Case study

We report a 13-year-old boy with a diagnosis of partial trisomy 9, global developmental delay, epilepsy, and challenging behaviour. Seizure onset was at 18 months of age, initially with fever. Multiple seizure types, without fever, emerged over the years: tonic-clonic, tonic, focal seizures, drops, and absences. His epilepsy was drug-resistant. He had failed treatment with sodium valproate, topiramate, levetiracetam, and ethosuximide. Seizures tended to cluster over a few days, usually with the need for rescue medication and frequent hospitalisations. At the time of the clusters, he would become less active, with reduced mobility and was not his usual self, though he could still eat and drink. These episodes were clinically suggestive of non-convulsive status, but had not been documented on EEG previously.

There was a partial response to short courses of oral prednisolone, with reduction in need for in-patient therapy.

He was admitted to the epilepsy monitoring unit for EEG-video telemetry, 48 hours into an habitual episode. He was sleeping excessively, very subdued, and would

briefly arouse, look around, and then go back to sleep (*video sequence 1*).

On examination, he was afebrile, with normal heart rate, blood pressure, and respiratory rate. There were no focal neurological deficits. Blood sugar was 4.3 mmol/l. EEG at that time was chaotic with continuous generalised 1.5-2.5-Hz sharp/spike and slow-wave complexes (*figure 1*). Both clinical and electrographic features were compatible with NCSE.

He had two doses of prednisolone, 40 mg per day, by the time he was admitted for telemetry. As he was still in non-convulsive status, he was given 10 mg buccal midazolam at 18:05 on Day 1 of admission. There was some clinical improvement in that he managed to drink 100 ml of juice and had some food. His EEG continued to show NCSE. On Day 2, he had two further tonic seizures at 01:21 and 04:45. The first episode was accompanied by desaturation to 57% and an increase in heart rate to 120 beats per minute. He was given another 10 mg of buccal midazolam at 06:00 on Day 2. He had three further tonic seizures at 09:45, 12:00 and 13:45 on Day 2. His EEG continued to indicate NCSE. Clobazam, at 10 mg, was given at 16:30 on Day 2. He continued to have more tonic seizures at 18:40 (on Day 2) and on Day 3 at 03:00, 08:55 and 11:00 (*figure 2*). There was no change in his level of alertness, interaction, or his EEG.

Therefore, on Day 3, at 11:19, a trial of clomethiazole (192-mg capsules of Heminevrin) was commenced; two capsules were given every four hours for 24 hours, then every six hours for 24 hours, every eight hours for 24 hours, and then treatment was stopped.

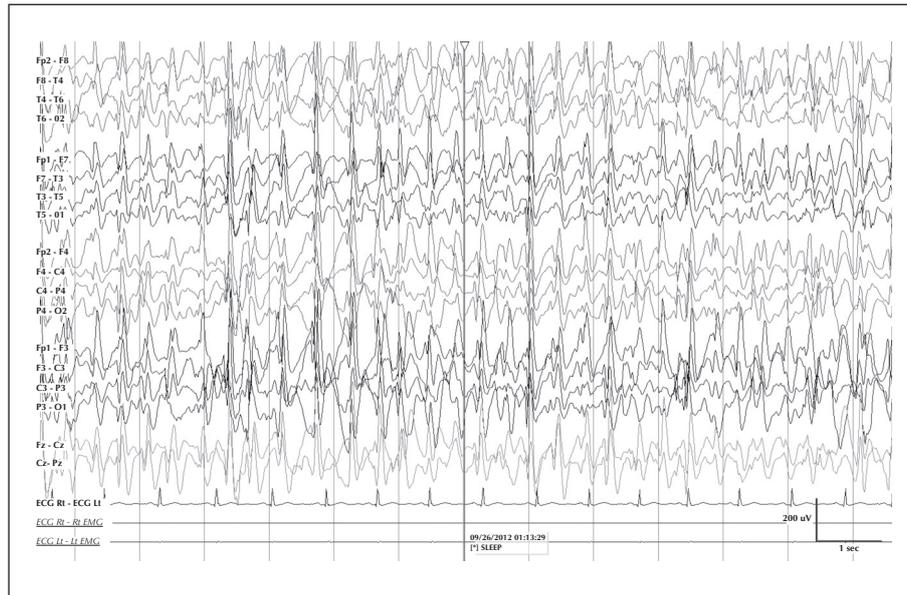


Figure 2. EEG recorded during sleep after treatment with buccal midazolam and before treatment with clomethiazole. This continues to show persistent generalised 1.5-2.5-Hz spike-wave discharges.

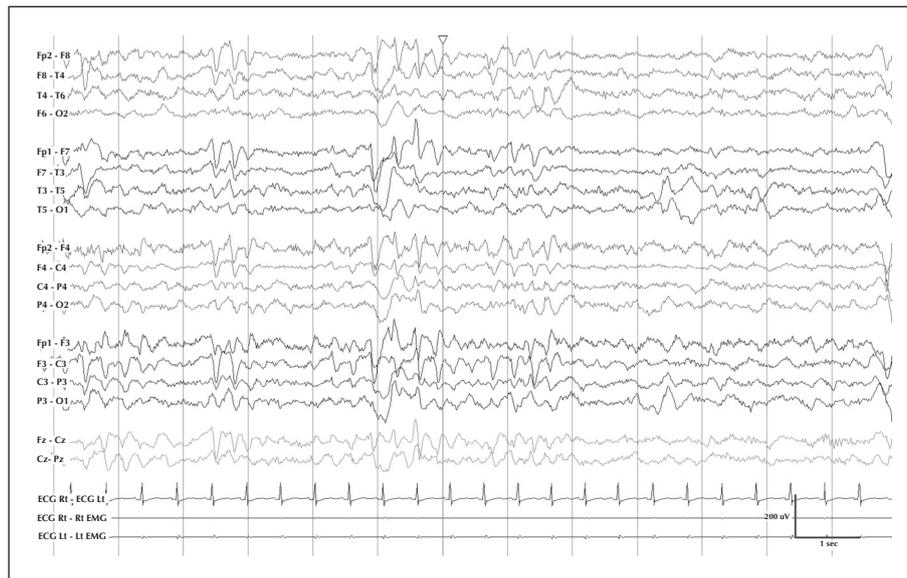


Figure 3. EEG recorded 24 hours after starting clomethiazole. This shows significant improvement with return of background rhythms and rare bifrontal discharges.

He did not have any further tonic seizures and the discharges started breaking up at 11:43 and were significantly reduced by four hours after commencing treatment. This resulted in a significant improvement in his functioning and level of alertness. On discharge, he continued to have occasional discharges on the EEG (*video sequence 2 and figure 3*).

There were no respiratory or cardiovascular side effects observed in the unit and none were reported

subsequently. He had mild ataxia. He was discharged home with a plan to use this regime as rescue if needed. The next cluster of seizures occurred 15 months after the above-described episode. The patient initially seemed to respond to a course of oral steroids but the patient relapsed with a cluster occurring within a week of stopping the steroids. This time, clomethiazole was given using the same regime described above. He had significant drowsiness and was not able to

move about. The mother reported that this occurred 20 minutes after taking the medication. By Day 3 of the course, he was more arousable, was still ataxic, but could move with assistance, and was eating and drinking. By Day 4, he started to move independently. He had a further cluster of seizures three months later with significant change in his baseline alertness and interaction. He was less active with reduced mobility and oral intake. This time, he was given a smaller cumulative dose. He was given two capsules (192 mg) every four hours for 12 hours, then two capsules every six hours for 24 hours, then two capsules every eight hours for 16 hours, then two capsules every 12 hours for 24 hours, and then treatment was stopped. The mother felt that he had tolerated this course better. Both the above seizure clusters were managed at home.

Discussion

This report describes the use of clomethiazole as an acute rescue therapy for NCSE. There are no consensus guidelines delineating optimal treatment of NCSE for ambulatory patients and there is a paucity of an evidence base (Ham and Waterhouse, 2012). This is reflected in the wide inter-physician variability in treatment approaches (Ham and Waterhouse, 2012).

Previous reports have suggested the use of intravenous clomethiazole for the treatment of NCSE (Ogren, 1986). Clomethiazole is a derivative of the thiazole nucleus of thiamine (vitamin B1). Evidence suggests that clomethiazole enhances GABA-ergic transmission in the brain by a mechanism which partly differs from that of the barbiturates and the benzodiazepines. Clomethiazole appears to act on an allosteric site of the GABA (A) receptor complex, which is closely related to chloride channel functions. Clomethiazole also enhances glycine-mediated inhibition. The action on the chloride channel function may be relevant to the anticonvulsant property of the drug (Ogren, 1986). Because of its anticonvulsant and sedative properties, clomethiazole has been used in the management of acute alcohol withdrawal, toxemia of pregnancy (Ogren, 1986), and CSE (Harvey *et al.*, 1975).

The first use of the drug was reported in 1963 (Poiré *et al.*, 1963) and was licensed for use in Europe at the same time. It was later reported to be effective for treating patients with status epilepticus, including those patients unresponsive to diazepam infusion (Poiré *et al.*, 1963). It was regularly used as second-line therapy for the treatment of CSE in the UK in the 1980s. There have been practical difficulties in using clomethiazole infusion, especially regarding its propensity to react with plastic and hence the need for frequently chang-

ing infusion sets. With the arrival of alternatives, its use for CSE diminished in the 1990s (Shorvon, 2009) and it is no longer a part of standard protocols (APLS, 2011). Clomethiazole can be given orally, but because it has a short half-life of 46 minutes, it must be given at frequent intervals. It is free of serious side effects and has little cardiorespiratory depressant action in therapeutic doses (Harvey *et al.*, 1975), although apnoea has been reported in a child after an excessive dose (Harvey *et al.*, 1975). Common side effects are drowsiness and ataxia following oral administration (Harvey *et al.*, 1975). These are short-lived and reversible, in keeping with the drug's short half-life.

Young Epilepsy is a specialised residential centre for children and young people with complex epilepsy. They have multiple comorbidities including autism, learning difficulties, and challenging behaviour. Intravenous cannulation can be difficult in this population and many are on regular benzodiazepines. Hence, clomethiazole has been used as an alternative oral drug when benzodiazepines were ineffective or could not be used in patients with either clusters of seizures or NCSE. Also, since this centre is over 30 minutes away from the nearest accident and emergency unit, there was concern of using repeated doses of benzodiazepines and risk of respiratory depression. Hence, clomethiazole was adopted as an alternative oral drug in the pre-hospital setting due to its non-respiratory depressant properties. There has been considerable experience in using this drug in our institution over the last 15 years with a very good safety profile. We use doses of one to two capsules (192 mg) every four hours for the first 24 hours, every six hours for the next 24 hours, and every eight hours for the following 24 hours. We then discontinue on Day 4. We usually use it for children more than 12 years of age. If they weigh more than 50 kg, we would use two capsules and if less than 50 kg, use one capsule. We have not experienced any serious adverse effects from the use of clomethiazole. The adverse effects usually noted are drowsiness and ataxia. We have not monitored renal function as this is not suggested in the British National Formulary (BNF) for children. We have had the opportunity to observe our patients carefully and our recommendation would be to use it, at least in the first instance, for inpatients in order to assess tolerability.

We have not been able to identify any literature describing the use of oral clomethiazole in the management of CSE or NCSE. This case report demonstrates the effective use of oral clomethiazole in treating NCSE, both in inpatient and outpatient settings, and the reduction of the need for hospital admission. Clomethiazole should be considered a safe oral option for management of NCSE when conventional treatment has failed.

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This work has not been presented in any meetings.

Legends for video sequence

Video sequence 1

Patient is in non-convulsive status. He is less alert, refuses to eat, and is making minimal eye contact.

Video sequence 2

Patient is no longer in non-convulsive status. He is making better eye contact and is more alert.

Keywords for the video research on www.epilepticdisorders.com

Syndrome: symptomatic epilepsy
Aetiology: chromosomal ; genetic
Phenomenology: non-convulsive status
Localization: not applicable

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TEST YOURSELF



- (1) What are the clinical features of non-convulsive status in children?
- (2) In which situations does non-convulsive status occur?

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".