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5% Carbon Dioxide is safe but of limited efficacy as a treatment for paediatric non-convulsive status epilepticus: an open label observational study

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Abstract

Objective
To establish the efficacy and tolerability of inhaled 5% carbon dioxide/95% oxygen as a treatment for paediatric non-convulsive status epilepticus (NCSE)

Methods
In an open label clinical trial, children in NCSE were given high flow inhaled 5% carbon dioxide/95% oxygen by face mask for 120 seconds under EEG control.

Results
Six children (five male; ages 3-13; all with severe underlying epilepsy and disability) were recruited. Inhalation was well tolerated in all cases. Capillary blood gasses showed no significant derangements at the end of the inhalation. Effects on EEG normalisation were limited and transient, and no clinical improvements were noted. No adverse effects occurred.

Conclusion
Inhaled 5% carbon dioxide/95% oxygen has been suggested as a potent, well tolerated anticonvulsant. An anticonvulsant without sedating and respiration-depressing effects would be particularly welcome in the management of NCSE where the justification for aggressive anticonvulsant therapy is often uncertain, however it appears that 5% carbon dioxide is of limited efficacy in this context.

Key words
Non-convulsive status epilepticus, children, carbogen, carbon dioxide, blood pH

Abbreviations
GCS  Glasgow Coma Scale
SE    Status epilepticus
NCSE  Non-convulsive status epilepticus
VFOs  Very fast oscillations
Introduction

Convulsive status epilepticus (SE) is a common neurological emergency at all ages. In children a population-based study estimated an incidence of 20 episodes per 100,000 children annually with a case fatality of 3% (1). The morbidity and mortality of convulsive SE relate to event duration (2) prompting the development of emergency treatment protocols to achieve prompt seizure termination. By contrast non-convulsive status epilepticus (NCSE) has received less attention, and is very probably under-diagnosed (3). Agreed operational definitions of NCSE are lacking but it comprises the presence of bilateral abnormal EEG activity consistent with seizures, without obvious motor manifestations. Waxing and waning of the EEG discharges and paroxysmal changes in the pattern and areas involved are commonly seen. The clinical manifestations of NCSE typically comprise variable and non-specific deteriorations in neurological function that may be global (i.e. reduced alertness and awareness) or more focal cognitive deficits (4). Various classifications of subtypes of NCSE have been suggested including atypical absence status, subclinical status, and minor motor status although these terms and their boundaries are not well defined.

NCSE is often associated with underlying neurological disease. In adults this association is primarily with acute, critical illness (5). In children the association is often with epilepsies associated with epileptic encephalopathy and severe neurodevelopmental disability. Examples of epilepsies frequently associated with NCSE in children include Dravet syndrome, ring chromosome 20 (6) and Lennox-Gastaut syndrome. All are associated with severe epilepsy and prior neurodevelopmental disability (7). The potential for NCSE to cause additional neurological morbidity in this context is controversial (8, 9). Children with epilepsies associated with NCSE (such as Dravet or Lennox-Gastaut syndromes) do tend to show increasingly evident developmental disability over time but it is not clear whether this is a consequence of episodes of NCSE per se, or reflects natural progression of the genetic and other mechanisms underlying the epilepsy. Due to the non-specific nature of the external manifestations, recognition of NCSE can be delayed sometimes for days or even weeks. These ambiguities raise practical dilemmas about the appropriate degree of aggressiveness of any intervention for NCSE, which remains an important challenge in paediatric neurological practice. Conventional treatments for SE are often sedating. Drowsiness can be an activator of NCSE and thus these treatments may be paradoxically unhelpful. More importantly sedating treatments have a high potential for respiratory complications and secondary morbidity – in children already at high risk of such complications — which have to be set against the potentially modest long term benefits of normalisation of the EEG.

The ideal drug for the treatment of both convulsive and non-convulsive SE would be of rapid onset, free of anaesthetic effects, maintain alertness and levels of respiratory and bulbar function and have a sustained duration of action. Induction of mild temporary respiratory acidosis has the potential to be an important adjunctive treatment in the treatment of NCSE by providing a rapid onset anticonvulsant action with minimal respiratory depression. A convenient way to achieve temporary mild respiratory acidosis is the inhalation of 5% carbon dioxide/95% oxygen, which has been reported to terminate recent-onset seizures in rats and non-human primates and has also been demonstrated to terminate acute onset focal seizures in preliminary clinical studies in adult humans (10). Anticonvulsant properties of inhaled carbon dioxide were first reported many years ago (11). This paper reports a phase I open label safety and tolerability study of inhaled 5% carbon dioxide/95% oxygen in NCSE in children.
Methods
Children were eligible for the study if they had an established diagnosis of epilepsy with either known aetiology, or were deemed to have undergone sufficient prior investigation to infer a cryptogenic/unknown (ILAE 2010) aetiology. The main purpose of this criterion was to mitigate the small risk of recruiting a child with an acute symptomatic seizure disorder, and in particular one associated with acute raised intracranial pressure (ICP) because of the theoretical concern that raising the partial pressure of carbon dioxide in arterial blood (PaCO2) by increasing the percentage of carbon dioxide in the inhaled air might further elevate ICP.

Children with clinically suspected NCSE commenced EEG monitoring using a standard 10-20 montage. Children were eligible if they had confirmed NCSE, defined as (i) bihemispheric, continuous or near-continuous, spike-wave or other features indicative of seizure activity on contemporaneous EEG and (ii) history from parent, or other familiar carer of a reduced level or function or awareness than normal.

The presence of subtle clinically evident seizure activity was not an exclusion criterion so long as the treating physician was satisfied that urgent treatment was not required. A baseline capillary blood gas was performed and children excluded if the capillary pCO2 was > 8kPa (60mmHg).

5% carbon dioxide/95% oxygen was delivered by loose fitting face mask retained by a parent or elastic. The gas was delivered at 15 litres/minute to ensure a large excess at the mouth and to avoid mixing the gas with entrained air on inspiration.

EEG recording commenced a minimum of 10 minutes before commencing the 5% carbon dioxide inhalation which was for 120 seconds. A provision in the protocol allowed for the premature discontinuation of inhalation if observers (including parents) felt it was any distress. At the end of the inhalation the child reverted to breathing room air. A capillary blood gas measurement was repeated at the end of the inhalation. EEG monitoring was continued for 20 minutes post inhalation. Alertness (assessed using the Glasgow Coma Scale, GCS), subjective assessments of breathlessness and distress, respiratory rate and pulse rate were documented before, during and at the end of inhalation.

Children were observed for 24h post inhalation and followed up by telephone or face to face contact on day 7.

Primary endpoints for the study were: the tolerated period of carbogen inhalation, incidence of adverse effects and recruitment rates. Secondary endpoints were the respiratory rate before and after inhalation, the capillary blood gas pH and PaCO2 at the end of inhalation and a qualitative assessment of the EEG for evidence of normalisation during and after administration.

The study received full research ethics review and approval (REC reference 12/NE/0005) and was registered as a clinical trial (EudraCT 2011-005318-12). Because final confirmation of eligibility required confirmation of NCSE on EEG, written “consent in principle” to participate in the study was obtained with final verbal consent to proceed once NCSE was confirmed electrographically and a baseline blood gas result excluded pre-existing respiratory failure.

The initial recruitment target (n=30) was based on the detection of adverse incidents with a true incidence of >10%. If no adverse effects are observed in 30 children the upper limit of a 95% confidence interval for the true proportion of adverse effects will is 11% (13). However despite the opening of additional centres recruitment was very slow and the study was closed by the Trial Steering Committee 30 months after the recruitment of the first child, on the basis that substantial increases in recruitment rates were unrealistic.
Results

Six children were recruited over 30 months. Patient details are shown in Table 1.

All children tolerated a full 120s inhalation. One non-verbal child was showing some mild apparent distress by the end of the inhalation however this immediately resolved on discontinuation. Capillary blood gas data pre- and post-inhalation were within acceptable ranges (Table 1).

Qualitative reports of the concurrent EEG recordings are shown in Table 2.

A semi-quantitative analysis was performed in five cases. Case five was excluded from this analysis as a 9 minute period of seizure freedom commenced just prior to inhalation and thus was probably coincidental. In the remaining five cases, the 120s epochs immediately prior, during and immediately after inhalation were divided into five second epochs, and the number of seconds of seizure freedom with re-appearance of some background activity within each epoch was noted. Periods of <1s duration were ignored. These are shown graphically in Figure 1.

No adverse events were noted within 7 days of inhalation.

Inhalation of 5% carbon dioxide/95% oxygen in this clinical context was safe and well tolerated. However the efficacy of the inhalation in normalising the EEG was limited. Case 1 showed no obvious change. In case 5 a prolonged period of seizure cessation coincided with but just preceded the onset of inhalation and was probably coincidental (Table 2). In the remaining four cases (2, 3, 4 and 6) quantitative analysis (Figure 1) suggested some temporary increase in the frequency of periods of seizure freedom however these periods were very brief and fragmented. Benefits typically reversed rapidly on discontinuation of inhalation.
Discussion

A number of lines of evidence indicate a potential role for brain pH in both seizure onset and termination. Seizure onset is preceded by the presence of very fast oscillations (VFOs) detectable both in vitro and in vivo electroencephalographic (EEG) recordings. VFOs probably result from inter-cellular connectivity mediated via gap junctions (14), which are known to be very pH sensitive, opening under conditions of alkalosis. A role for acid-sensing ion channel 1 (ASIC1) in the mechanism of seizure termination by acidosis has been suggested (15). Respiratory alkalosis caused by hyperventilation has long been recognised as a trigger of a specific childhood epilepsy syndrome (Childhood Absence Epilepsy, CAE) and it has also been suggested that fever-induced hyperventilation may contribute to the occurrence of the common paediatric phenomenon of fever-associated seizures (“febrile convulsions”) (16,17). Conversely respiratory acidosis achieved by rebreathing of expired air has been reported to terminate febrile seizures (18).

The data on tolerability this study provides is useful. The physiological consequences of 5% carbon dioxide inhalation are comparable to rebreathing exhaled air using a paper bag, or holding one’s breath. The primary adverse effect of inhalation of carbon dioxide is a concentration- and duration-dependent sense of an urgent need to breathe, or “air hunger”. Brief inhalations of higher concentrations of carbon dioxide (9-35%) have been used as experimental models of panic attacks (19). Our data suggest that 120s inhalations are tolerated by this group of severely disabled, non-verbal children.

The lack of efficacy seen in this study contrasts with reports in adults with acute-onset focal seizures (10). This may reflect the much more severe underlying neurological disorders in this study population (Table 1). It may also relate to the often-delayed recognition of NCSE, meaning that states of abnormal cortical dynamics are long-established at the time of attempted treatment. Although a continuous slow theta activity is characteristic of Angelman syndrome, in both cases 3 and 4 the children were clinically symptomatic with increased encephalopathy (the indication for the EEG) and EEG showed unambiguous spike-wave activity: we therefore regard it as appropriate to regard them as being “in NCSE” at the time of the study.

Both PaCO2 and blood pH are under tight physiological homeostatic control. Increasing the proportion of CO2 in inspired air will trigger multiple homeostatic mechanisms to renormalise blood pH including a hyperventilation response and carbonic anhydrase based buffering responses: thus it is probably more appropriate to regard the intervention as causing a pH transient, at least in blood pH (reflected by the fact that all capillary blood pH measurements were normal at the end of 120s inhalation, Table 1). Much less is known about the time course of any resulting changes in intra-cerebral pH. It is possible that longer periods of inhalation could have been more beneficial. Although our study protocol did allow for review and possible extension by the Trial Steering and Data Monitoring Committees of the inhalation period this was overtaken by the decision to close the trial on grounds of slow recruitment. As an alternative to longer periods of inhalation of 5% carbogen, a higher percentage CO2 inhalation mixture could have been used: however as discussed above, rates of distress due to subjective “air hunger” would probably be higher.

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

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Legends to Figures and Tables

Table 1. Characteristics of study participants

Details of study participants, with capillary blood gas and respiratory rate parameters pre and post inhalation of 5% carbon dioxide/95% oxygen for 120s.

Table 2. Qualitative interpretation of EEG

Qualitative (unblinded) interpretation of EEG changes

Figure 1. Quantitative analysis of EEG

Quantitative analysis of EEG changes pre, during and post inhalation. Case 5 is not shown (see Results). For the remaining five cases the thick vertical line at time t=0 delineates the commencement, and the dotted vertical line at time t=120s the end, of the inhalation period. Y-axis displays the number of seconds of seizure activity per five second epoch (i.e. downward displacement of the line reflects improvement in the EEG).
<table>
<thead>
<tr>
<th>Case</th>
<th>Gender</th>
<th>Aetiology</th>
<th>Age (yrs)</th>
<th>Blood pH (Baseline, End inhalation)</th>
<th>Capillary pO2 (Baseline, End inhalation)</th>
<th>Capillary pCO2 (Baseline, End inhalation)</th>
<th>Resp rate (Baseline, End inhalation)</th>
<th>Distress?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3M</td>
<td>Lissencephaly (PAFAH1B1 mutation)</td>
<td>7.38</td>
<td>7.37</td>
<td>5.13</td>
<td>12.34</td>
<td>5.09</td>
<td>5.31</td>
</tr>
<tr>
<td>2</td>
<td>13M</td>
<td>Alper mitochondrial depletion syndrome</td>
<td>7.38</td>
<td>7.46</td>
<td>6.10</td>
<td>14.30</td>
<td>4.50</td>
<td>4.10</td>
</tr>
<tr>
<td>3</td>
<td>5M</td>
<td>Angelman</td>
<td>7.38</td>
<td>7.37</td>
<td>9.56</td>
<td>13.21</td>
<td>5.11</td>
<td>4.89</td>
</tr>
<tr>
<td>4</td>
<td>4M</td>
<td>Angelman syndrome</td>
<td>7.40</td>
<td>7.44</td>
<td>8.49</td>
<td>11.95</td>
<td>5.45</td>
<td>5.44</td>
</tr>
<tr>
<td>5</td>
<td>10F</td>
<td>Lissencephaly</td>
<td>7.41</td>
<td>7.42</td>
<td>7.79</td>
<td>7.10</td>
<td>5.45</td>
<td>5.50</td>
</tr>
<tr>
<td>6</td>
<td>5M</td>
<td>Septo-optic dysplasia</td>
<td>7.45</td>
<td>NK</td>
<td>9.59</td>
<td>NK</td>
<td>4.19</td>
<td>NK</td>
</tr>
</tbody>
</table>
Table 2. Qualitative interpretation of EEG

<table>
<thead>
<tr>
<th>Case</th>
<th>Pre</th>
<th>During inhalation (120 seconds)</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Epileptic encephalopathy with bursts of high amplitude multifocal disorganised spike and wave alternating with periods of relatively or very suppressed background</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>2</td>
<td>High amplitude continuous sharp and slow wave activity mainly over the right; reasonably synchronous and well organized; approx. 1.5Hz</td>
<td>Some reduction in amplitude after 45s; brief seizure free periods of a few seconds</td>
<td>Rapid reversion to pre-inhalation pattern</td>
</tr>
<tr>
<td>3</td>
<td>Continuous reasonably well organised seizure activity maximal posteriorly with intermittent spread anteriorly</td>
<td>Some attenuation of activity after 45s; brief epochs of seizure freedom</td>
<td>Some persistence of improved appearances</td>
</tr>
<tr>
<td>4</td>
<td>Long runs of anteriorly-predominant, synchronous sharp and slow wave activity of up to approximately 90 seconds with brief interruptions to reveal relatively normal background.</td>
<td>No convincing change</td>
<td>No change</td>
</tr>
<tr>
<td>5</td>
<td>Long runs of seizure activity with temporal-parietal predilection but spread to the left. Some periods of spontaneous remission of seizure activity of up to 8 mins before carbogen exposure. Seizure activity seen shows a relatively organised synchronous sharp and slow wave discharge with a repeating frequency of just under 2Hz At times independent seizure activity is seen over the left hemisphere in the temporal-parietal region also.</td>
<td>Seizure free for 9 mins however this appeared to begin just prior to start of inhalation</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Long runs of seizure activity affecting predominantly the right hemisphere (sharp and slow wave activity ~2Hz). Brief periods of seizure freedom lasting up to approximately 10 seconds.</td>
<td>Amplitude of seizure activity reduces and periods of 5-10 seconds seizure freedom.</td>
<td>Reversion to pre-inhalation pattern</td>
</tr>
</tbody>
</table>
Figure 1. Quantitative analysis of EEG
References


Banaji M, Mallet A, Elwell CE, Nicholls P, Cooper CE. A Model of