Forsyth R, Martland T, Lai M, Vadlamani G, Hogan V.

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

European Journal of Paediatric Neurology 2016, 20(4), 560-565.

Copyright:

© 2016. This manuscript version is made available under the [CC-BY-NC-ND 4.0 license](#)

DOI link to article:

<http://dx.doi.org/10.1016/j.ejpn.2016.04.001>

Date deposited:

17/08/2016

Embargo release date:

22 April 2017

This work is licensed under a

[Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International licence](#)

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

Rob Forsyth^{1,2}
Tim Martland³
Ming Lai⁴
Gayatri Vadlamani⁵
Vanessa Hogan⁶

¹Institute of Neuroscience, Newcastle University, Newcastle upon Tyne NE1 7RU

²Great North Children's Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle NE1 4LP

³Department of Paediatric Neurology, Royal Manchester Children's Hospital, Oxford Road, Manchester M13 9WL

⁴Department of Neurophysiology, Royal Victoria Infirmary, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle NE1 4LP

⁵Department of Paediatric Neurology, Leeds General Infirmary, Great George Street, Leeds LS1 3EX

⁶Newcastle Clinical Trials Unit, Institute of Health and Society, Newcastle University, Newcastle upon Tyne NE1 7RU

Correspondence to

Dr Rob Forsyth, Institute of Neuroscience, Sir James Spence Institute, Royal Victoria Infirmary, Newcastle University, NE1 4LP, Newcastle upon Tyne, Newcastle, UK.

Tel: +44 191 282 5742

Fax: +44 191 282 4878

Email: rob.forsyth@newcastle.ac.uk

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 an cryptogenic/unknown (ILAE 2010 (12) 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 be 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.

This work was funded by a grant from Epilepsy Research UK (P1103). The funder had no role in the study design; collection, analysis and interpretation of data; the writing of the report; or in the decision to submit the article for publication.

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 1. Characteristics of study participants

Case	Age (yrs) , gender	Aetiology	Blood pH		Capillary pO2		Capillary pCO2		Resp rate		Post Inhalation Distress?
			Baseline	End inhalation	Baseli ne	End inhalation	Baseli ne	End inhalation	Baseline	End inhalation	
1	3M	Lissencephaly (PAFAH1B1 mutation) Alper mitochondrial depletion syndrome	7.38	7.37	5.13	12.34	5.09	5.31	40	40	No
2	13M	(POLG1 mutation)	7.38	7.46	6.10	14.30	4.50	4.10	28	30	No
3	5M	Angelman	7.38	7.37	9.56	13.21	5.11	4.89	14	21	Temporary mild
4	4M	Angelman syndrome	7.40	7.44	8.49	11.95	5.45	5.44	25	20	No
5	10F	Lissencephaly	7.41	7.42	7.79	7.10	5.45	5.50	16	22	No
6	5M	Septo-optic dysplasia	7.45	NK	9.59	NK	4.19	NK	24	24	No

Table 2. Qualitative interpretation of EEG

Case	Pre	During inhalation (120 seconds)	Post
1	Epileptic encephalopathy with bursts of high amplitude multifocal disorganised spike and wave alternating with periods of relatively or very suppressed background	No change	No change
2	High amplitude continuous sharp and slow wave activity mainly over the right; reasonably synchronous and well organized; approx. 1.5Hz	Some reduction in amplitude after 45s; brief seizure free periods of a few seconds	Rapid reversion to pre-inhalation pattern
3	Continuous reasonably well organised seizure activity maximal posteriorly with intermittent spread anteriorly	Some attenuation of activity after 45s; brief epochs of seizure freedom	Some persistence of improved appearances
4	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.	No convincing change	No change
5	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.	Seizure free for 9 mins however this appeared to begin just prior to start of inhalation	
6	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.	Amplitude of seizure activity reduces and periods of 5-10 seconds seizure freedom.	Reversion to pre-inhalation pattern

Figure 1. Quantitative analysis of EEG

References

1. Chin RFM, Neville BGR, Peckham C, Bedford H, Wade A, Scott RC, et al. Incidence, cause, and short-term outcome of convulsive status epilepticus in childhood: prospective population-based study. *Lancet*. 2006;368(9531): 222-229. Available from: doi:10.1016/S0140-6736(06)69043-0
2. Shorvon S. The outcome of tonic-clonic status epilepticus. *Current opinion in neurology*. 1994;7(2): 93-95.
3. van Rijckevorsel K, Boon P, Hauman H, Legros B, Osseman M, Sadzot B, et al. Standards of care for non-convulsive status epilepticus: Belgian consensus recommendations. 2006. pp. 117-124.
4. Deonna T, Davidoff V, Medar-Ingvar M, Zesiger P, Marcoz J-P. The spectrum of acquired cognitive disturbances in children with partial epilepsy and continuous spike-waves during sleep. *European Journal of Paediatric Neurology*. 1997;1: 19-29.
5. Maganti R, Gerber P, Drees C, Chung S. Nonconvulsive status epilepticus. *Epilepsy & behavior : E&B*. [Online] 2008;12(4): 572-586. Available from: doi:10.1016/j.yebeh.2007.12.002
6. Jacobs J, Bernard G, Andermann E, Dubeau F, Andermann F. Refractory and lethal status epilepticus in a patient with ring chromosome 20 syndrome. *Epileptic disorders : international epilepsy journal with videotape*. [Online] 2008;10(4): 254-259. Available from: doi:10.1684/epd.2008.0212
7. Wirrell E, Farrell K, Whiting S. The epileptic encephalopathies of infancy and childhood. *The Canadian journal of neurological sciences Le journal canadien des sciences neurologiques*. 2005;32(4): 409-418.
8. Aminoff MJ. Do nonconvulsive seizures damage the brain?--No. *Archives of Neurology*. 1998;55(1): 119-120.
9. Young GB, Jordan KG. Do nonconvulsive seizures damage the brain?--Yes. *Archives of Neurology*. 1998;55(1): 117-119.
10. Tolner EA, Hochman DW, Hassinen P, Otahal J, Gaily E, Haglund MM, et al. Five percent CO₂ is a potent, fast-acting inhalation anticonvulsant. *Epilepsia*. [Online] Blackwell Publishing Ltd; 2011;52(1): 104-114. Available from: doi:10.1111/j.1528-1167.2010.02731.x
11. Lennox WG. The effect on epileptic seizures of varying the composition of the respired air. *J Clin Invest*. 1928; 6: 23-24.
12. Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, Van Emde Boas W, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. *Epilepsia*. [Online] 2010;51(4): 676-685. Available from: doi:10.1111/j.1528-1167.2010.02522.x

13. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. *Statistics in medicine*. 1998;17(8): 857-872.
14. Traub RD, Whittington MA, Buhl EH, LeBeau FE, Bibbig A, Boyd S, et al. A possible role for gap junctions in generation of very fast EEG oscillations preceding the onset of, and perhaps initiating, seizures. *Epilepsia*. 2001;42(2): 153-170.
15. Ziemann AE, Schnitzler MK, Albert GW, Severson MA, Howard MA, Welsh MJ, et al. Seizure termination by acidosis depends on ASIC1a. *Nature Neuroscience*. [Online] 2008;11(7): 816-822. Available from: doi:10.1038/nn.2132
16. Schuchmann S, Schmitz D, Rivera C, Vanhatalo S, Salmen B, Mackie K, et al. Experimental febrile seizures are precipitated by a hyperthermia-induced respiratory alkalosis. *Nature medicine*. [Online] 2006;12(7): 817-823. Available from: doi:10.1038/nm1422
17. Schuchmann S, Hauck S, Henning S, Grüters-Kieslich A, Vanhatalo S, Schmitz D, et al. Respiratory alkalosis in children with febrile seizures. *Epilepsia*. [Online] 2011;52(11): 1949-1955. Available from: doi:10.1111/j.1528-1167.2011.03259.x
18. Schuchmann S, Schmitz D, Grüters-Kieslich A, Vanhatalo S, Kaila K. Suppression of complex febrile seizures by elevating respiratory CO2 using re-breathing technique - two case reports. *Epilepsia*. 2009;50(Suppl. 4): 262.
19. Colasanti A, Salamon E, Schruers K, van Diest R, van Duinen M, Griez EJ. Carbon dioxide-induced emotion and respiratory symptoms in healthy volunteers. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*. [Online] 2008;33(13): 3103-3110. Available from: doi:10.1038/npp.2008.31
20. Mendenhall WM, Morris CG, Amdur RJ, Mendenhall NP, Siemann DW. Radiotherapy alone or combined with carbogen breathing for squamous cell carcinoma of the head and neck: a prospective, randomized trial. *Cancer*. [Online] Wiley Subscription Services, Inc., A Wiley Company; 2005;104(2): 332-337. Available from: doi:10.1002/cncr.21146
21. Aquino-Parsons C, Lim P, Green A, Minchinton AI. Carbogen inhalation in cervical cancer: assessment of oxygenation change. *Gynecologic oncology*. [Online] 1999;74(2): 259-264. Available from: doi:10.1006/gyno.1999.5443
22. Aquino-Parsons C, Hukin J, Green A. Concurrent carbogen and radiation therapy in children with high-risk brainstem gliomas. *Pediatric blood & cancer*. [Online] 2008;50(2): 397-399. Available from: doi:10.1002/pbc.21057
23. Smeets EEJ, Julu POO, van Waardenburg D, Engerström IW, Hansen S, Apartopoulos F, et al. Management of a severe forceful breather with Rett syndrome using carbogen. *Brain & Development*. [Online] 2006;28(10): 625-632. Available from: doi:10.1016/j.braindev.2006.04.010
24. Banaji M, Mallet A, Elwell CE, Nicholls P, Cooper CE. A Model of

Brain Circulation and Metabolism: NIRS Signal Changes during Physiological Challenges. Sporns O (ed.) *PLoS Computational Biology*. [Online] 2008;4(11): e1000212-e1000215. Available from: doi:10.1371/journal.pcbi.1000212