Current Literature
In Clinical Science

Stopping Seizures With Carbon Dioxide

Five Percent CO_2 Is a Potent, Fast-Acting Inhalation Anticonvulsant.

Tolner EA, Hochman DW, Hassinen P, Otáhal J, Gaily E, Haglund MM, Kubová H, Schuchmann S, Vanhatalo S, Kaila K. *Epilepsia* 2011;52(1):104–114.

PURPOSE: CO_2 has been long recognized for its anticonvulsant properties. We aimed to determine whether inhaling 5% CO_2 can be used to suppress seizures in epilepsy patients. The effect of CO_2 on cortical epileptic activity accompanying behavioral seizures was studied in rats and nonhuman primates, and based on these data, preliminary tests were carried out in humans. METHODS: In freely moving rats, cortical afterdischarges paralleled by myoclonic convulsions were evoked by sensorimotor cortex stimulation. Five percent CO_2 was applied for 5 min, 3 min before stimulation. In macaque monkeys, hypercarbia was induced by hypoventilation while seizure activity was electrically or chemically evoked in the sensorimotor cortex. Seven patients with drug resistant partial epilepsy were examined with video-EEG (electroencephalography) and received 5% CO_2 in medical carbogen shortly after electrographic seizure onset. RESULTS: In rats, 5% CO_2 strongly suppressed cortical afterdischarges, by approximately 75%, whereas responses to single-pulse stimulation were reduced by about 15% only. In macaques, increasing pCO_2 from 37 to 44–45 mm Hg (corresponding to inhalation of 5% CO_2 or less) suppressed stimulation-induced cortical afterdischarges by about 70% and single, bicuculline-induced epileptiform spikes by approximately 25%. In a pilot trial carried out in seven patients, a rapid termination of electrographic seizures was seen despite the fact that the application of 5% CO_2 was started after seizure generalization. CONCLUSIONS: Five percent CO_2 has a fast and potent anticonvulsant action. The present data suggest that medical carbogen with 5% CO_2 can be used for acute treatment to suppress seizures in epilepsy patients.

Commentary

Although it has been known for more than 80 years that inhalation of an increased concentration of CO_2 may suppress seizures (1, 2), this phenomenon has not been exploited as a clinical treatment. Nonetheless, there is extensive experimental and clinical literature documenting that CO_2 concentrations of 10% and above can block or terminate a variety of seizures in animals and humans (3, 4), including electroshock seizures in psychiatric patients (5). The purpose of the current study by Tolner and colleagues is not only to revive attention for this neglected area of investigation but also to demonstrate the efficacy of 5% CO_2, a clinically appropriate concentration, and to carry out a preliminary study of this intervention to treat acute seizures in the epilepsy monitoring unit.

For the experimental animals in this study, hypercapnia was induced by pumping 5% CO_2 in air into a chamber holding the rats, or, in the macaques, by hypoventilation with artificial ventilation to adjust the pCO_2 to the level that would be expected from breathing 5% CO_2. Spontaneous seizures were not studied in animals. Rather, these interventions were shown to shorten afterdischarges induced by electrical cortical stimulation in both the rats and monkeys and reduce the amplitude and frequency of spikes induced by application of bicuculline to motor cortex. Acetazolamide produced a similar, but smaller, shortening of afterdischarges in the rats.

The human trial was done in patients with medically intractable localization-related epilepsy. Four patients were monitored with scalp electrodes, and three with subdural electrode arrays. As soon as possible after the electrographic seizure discharge spread bilaterally, a mixture of 5% CO_2 and 95% O_2 was applied by mask and then stopped when the seizure terminated. While 13 seizures were treated, 7 seizures from 5 of these patients were chosen as control events because they had semiology similar to the treated seizures. Application of the gas occurred at a mean of 40 seconds after the beginning of the electrographic seizures, and seizure duration was reduced by an average of 30% compared with the seven selected untreated seizures. No monitoring of pCO_2 or pO_2 is described.

It appears that hypercapnia suppresses and terminates seizures by altering pH, rather than by affecting cerebral blood flow. The antiepileptic effects of acetazolamide may also be due to lowering of brain pH (6). Moreover, respiratory alkalosis may be responsible for the activating effects of hyperventilation on epileptiform activity, and for fever-induced seizures (7). These facts indicate the need for clinicians to avoid respiratory alkalosis when ventilating patients with status epilepticus and other acute severe seizures.

In vivo studies demonstrate strong inhibition of neuronal activity with acidosis (8). This may be mediated by direct ac-

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tions on voltage and ligand-gated ion channels (9). There is an acid-sensing ion channel (ASIC1a) which regulates neuronal excitability with exquisite sensitivity to extracellular pH. There is evidence that acidosis activates inhibitory interneurons through ASIC1a (9). In addition, there is evidence that lowering of intracellular pH leads to increased extracellular adenosine, activation of adensosine A1 receptors and a decrease in excitatory synaptic transmission (10). This leads to decreased burst firing in a hippocampal slice seizure model. All of these mechanisms play a part in the self-termination of experimental seizures; it is logical that they would be activated more strongly with lowering of cerebral pH from respiratory acidosis.

The antiepileptic properties of hypercapnia are convincingly demonstrated by the published experimental and clinical studies, and the present study demonstrates its feasibility as a clinical treatment. Its introduction into everyday practice would first require a randomized controlled trial to demonstrate efficacy and safety. Patients could be randomized between 100% O_2 and the mixture of 5% CO_2 and 95% O_2 in a blinded fashion, with an adequate number of events treated to address the typical wide variability of spontaneous seizure duration and evolution. Safety monitoring should include measurement of pCO_2, to ensure that unsafe exacerbation of hypercapnia and systemic acidosis does not occur with any prolonged convulsive seizures that are refractory to the treatment. Such a clinical trial is realistic and worthwhile. Carbon dioxide inhalation could prove to be an easy and inexpensive intervention for acute seizures in the hospital, and possibly in the home as well.

by John W. Miller, MD, PhD

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