Original articles

The clinical incidence of central nervous system oxygen toxicity at 284 kPa (2.8 ATA)

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Key words
Hyperbaric oxygen, toxicity, hyperbaric facilities

Abstract

(Wilkinson D, Wright S, Goble S. The clinical incidence of central nervous system oxygen toxicity at 284 kPa (2.8 ATA). *SPUMS J*. 2005; 35: 120-4.)
Introduction: Central nervous system (CNS) oxygen toxicity is a recognised complication of hyperbaric oxygen treatment (HBOT), manifest most profoundly as a seizure. Reports have varied in the frequency of this complication.
Methods: A retrospective review of the computerised database of the Hyperbaric Medicine Unit at the Royal Adelaide Hospital was performed from 1986 to 2003. Symptoms attributed to CNS oxygen toxicity and the occurrence of seizure were both recorded for all patient treatments at 284 kPa (2.8 ATA).
Results: 1,395 patients received a total of 6,084 treatments at 284 kPa. Symptoms of CNS toxicity occurred in 64 treatments (1%) and seizure in 17 (0.3%). Incidence of seizure was significantly higher for emergency medical indications as compared with non-emergency medical indications. The highest incidence was found in the 1,493 treatments for decompression sickness (DCS) with symptoms in 32 (2%) and seizure in eight (0.5%). A gender disparity was observed, with an increased incidence of seizure in female divers that was not statistically significant. Of the eight seizures, seven occurred during the first treatment giving a risk of seizure during the first treatment for DCS of 1.80% or 1 in 55 patients.
Conclusions: An incidence of CNS oxygen toxicity at 284 kPa has been described for one hyperbaric facility. There is an increased risk of seizure in emergency compared with non-emergency medical treatments. There appears to be an increased risk of seizure in female divers and during the first recompression treatment for DCS.

Introduction

Hyperbaric oxygen treatment (HBOT) exposes a patient to potentially toxic levels of oxygen with effects on many organ systems. Within the central nervous system (CNS) oxygen toxicity can become manifest in a myriad of symptoms, or more dramatically as a seizure. The incidence of such complications has been difficult to interpret. Published papers have treated different patients under different conditions leading to a range of seizure incidence from 5 per 52,758 treatments (0.009%) to 3% of patients.[1,2] No other study has specifically reported the incidence of CNS oxygen toxicity with 284 kPa (2.8 ATA) exposures.

Methods

Research ethics committee approval was obtained for a retrospective review of the computerised treatment records of the Hyperbaric Medicine Unit from 1 January 1986 to 1 October 2003. For all patient exposures to an oxygen partial pressure of 284 kPa, database entry of symptoms attributable to CNS oxygen toxicity and occurrence of seizure were recorded. Treatment was provided in one of two twin-lock, multi-place chambers: either a 1.8-metre-diameter cylindrical chamber (Drägerwerk, Germany; 1985) or, since becoming available in 1994, a rectangular chamber (Cowan Manufacturing/Fink International, Australia; 1994). Oxygen was delivered by a built-in breathing circuit using either a head hood on continuous flow or a demand-regulator Scott™ mask (both Amron International, Escondido, CA, USA).

The clinical indications for HBOT treatment were recorded as diving or non-diving, and the non-diving medical indications divided into emergency and non-emergency categories. An emergency was considered to be a condition associated with a clinically significant alteration in normal physiology and included carbon monoxide, gas and smoke inhalation, acute infection, mucormycosis, thermal burn, traumatic and ischaemic injury and iatrogenic gas embolism. Non-emergency indications included chronic infection and osteomyelitis, non-healing wounds, radiation tissue injury, spider bite and other.

Results

A total of 1,395 patients received 6,084 treatments with oxygen at 284 kPa. Symptoms of CNS toxicity occurred in 64 treatments (1.05%) and seizure in 17 treatments (0.28%) (Table 1). Table 1 summarises the clinical indications for HBOT treatment together with the frequency of CNS oxygen toxicity (reported symptoms or seizures) in each category.

Table 1
Conditions treated and the frequency of CNS toxicity symptoms and seizures

Indication	Patients	Treatments	CNS symptoms	%	Seizures	%
Decompression sickness	388	1,493	32	2.14	8	0.54
CAGE (Diving)	23	90	-	-	-	-
Iatrogenic gas embolism	16	53	-	-	2	3.77
Carbon monoxide, gas/smoke inhalation	502	1,497	18	1.2	3	0.20
Acute infection	233	853	4	0.47	2	0.23
Chronic infection, osteomyelitis	39	660	1	0.15	-	-
Thermal burns	56	393	2	0.51	1	0.25
Traumatic, ischaemic injury	47	261	1	0.38	-	-
Radiation tissue injury	30	357	1	0.28	-	-
Wound healing	30	172	-	-	-	-
Mucormycosis	6	120	1	0.83	1	0.83
Spider bite	13	44	4	9.10	-	-
Other	12	91	-	-	-	-
Medical (emergency)	860	3,177	26	0.82	9	0.28
Medical (non-emergency)	124	1,324	6	0.45	-	-

Of 388 divers treated for DCS, eight experienced seizures over the 18 years of review. While noting an increased incidence of seizure in divers with decompression sickness (DCS) compared to medical indications, analysis of proportions failed to demonstrate statistical significance ($\chi^2 = 7.5$, df = 3, $p \leq 0.10$). When looking at the medical treatments in isolation, seizure risk is significantly increased for emergency compared with non-emergency indications ($\chi^2 = 3.76$, df = 1, p = 0.05).

To investigate any change in incidence of seizure in divers over time, they were chronologically arranged and divided into successive cohorts of 100 (the number of seizures in successive cohorts were three, three, one and one). Analysis suggested no significant change in incidence between successive groups ($\chi^2 = 1.8$, df = 3, $p < 1$). The characteristics of the eight divers who experienced these eight seizures are found in Table 2. Among 302 male divers a total of four seizures were experienced, while only 86 female divers experienced a total of four seizures among them. This trend towards increased seizure incidence in females did not reach statistical significance ($\chi^2 = 3.67$, df = 1, p = 0.55). Of note, seven of the eight seizures occurred during the first exposure to oxygen at 284 kPa.

Table 2
Characteristics of divers with decompression sickness (DCS) experiencing seizure

Age (years)	Sex	Treatment number	Treatment profile	Time of seizure
36	Male	1 of 1	18:60:30	Not stated
21	Female	1 of 2	USN 6	Not stated
22	Female	1 of 1	18:60:30	25 min
29	Female	1 of 3	USN 6	41 min
27	Male	1 of 3	USN 6	43 min
32	Male	1 of 1	18:60:30	35 min
22	Female	2 of 3	18:60:30	Not stated
40	Male	1 of 5	USN 6	55 min

Discussion

This study provides an incidence for symptoms and seizures attributable to CNS oxygen toxicity for hyperbaric chamber exposures to an oxygen partial pressure of 284 kPa. There is an issue of reliability in the reporting of symptoms of oxygen toxicity. Reported symptoms included nausea, feeling light-headed, agitation, shakes, feeling faint, sweating, tinnitus and numb lips. By their nature, such symptoms are not specific for oxygen toxicity and may be due to many other things; however, clinical practice does not advocate waiting for progression to seizure to confirm the diagnosis. If the symptoms are self-limited they may be considered trivial and not be reported by the patient, nor entered in the database. On the other hand, the incidence of seizure should be a reliable measure of CNS oxygen toxicity because seizure is an objective sign most likely to be due to oxygen toxicity and very likely to be recorded in the treatment record. It is reassuring to observe that the incidence of symptoms did loosely follow the trend observed with seizure. These results also suggest that the risk of seizure due to oxygen toxicity is not uniform for all indications. Subsequent discussion will separately consider diving and medical indications.

Treatment of DCS at 284 kPa has an incidence of 2% for symptoms of CNS toxicity, and 0.5% for seizure. Of note is the gender disparity favouring seizure in female divers. Only

one other group has reported a gender influence on the incidence of seizure in a published study and subsequent abstract.[3,4] The abstract reported an increased sample size of 2,303 recompressions in 1,073 patients with decompression illness. Oxygen partial pressures were in the range of 243–294 kPa and included US Navy Treatment Table 6 as well as other mixed-gas, deep tables. The incidence was a surprisingly comparable 2% for symptoms and 0.6% for seizure. Again, the researchers found that the risk of seizure in the female divers was 2.9 times that for males although this did not reach statistical significance either. For all the investigation into the myriad factors considered to be a risk for oxygen toxicity, no other clinical or laboratory research has been published on the influence of gender, and this indicates a need for further work.

The other striking feature of this study is the 'first-treatment effect' with seven of the eight seizures occurring during the first exposure. This gives an incidence of seizure during the first treatment for DCS of 1.8% or 1 in 55 divers. Corroborating evidence for an increased risk during the first treatment has not been published. Gender aside, are there any other patient factors that might influence the risk of seizure, particularly during the first exposure? One plausible theory is that DCS produces a neurological injury rendering the diver more susceptible to CNS toxicity – it would seem reasonable that bubbles passing through the cerebral circulation should have a significant impact. It was for this reason that the terminology of DCS and cerebral artery gas embolism (CAGE) was used to describe divers in this study.

If acute neurological injury is believed to increase the risk for CNS oxygen toxicity, one would expect to see evidence for this in diving-related CAGE. In this study, there was a zero incidence for symptoms and seizures in divers with CAGE, although small numbers may be responsible. However, contrast this with two seizures in 53 treatments for iatrogenic gas embolism. In any case, such a neurological injury would have to recover quickly as the risk appears to relate to the first treatment only. Of the eight divers who experienced seizure, five received subsequent HBOT treatment without further seizure.

Patient factors do not adequately explain the seizure risk. Other factors that may influence the development of oxygen toxicity include method of oxygen delivery (and carbon dioxide, CO_2, elimination) and the chamber environment itself. All treatments were undertaken at an ambient pressure of 284 kPa with the intention of delivering 100% oxygen; however, oxygen delivery may vary with the use of either mask or hood. The use of the rigid Scott mask requires attention to the fit of the mask around the face and proper fastening of the straps. Any gaps will allow air entrainment and unpublished data from this unit have demonstrated that the mask can deliver variable inspired oxygen content (80–95%), whereas the hood system provides reliably greater than 96% oxygen. This is consistent with published experience.[5]

With this in mind, it would be expected that use of the hood, with its higher oxygen content and therefore higher oxygen partial pressure, should carry an increased risk of CNS toxicity. This in fact appears not to be the case, as all seizures occurred in divers using the mask, although it must be remembered that 90% of all DCS treatments used the mask. Perhaps the mask alters risk via an effect on another known risk factor: CO_2. While the volume of the mask is small, re-breathing of CO_2 will occur to some degree although its significance is uncertain. Alternatively, as the mask delivers oxygen by demand valve, its use may unconsciously provoke 'skip-breathing' by the diver resulting in CO_2 retention and increased seizure risk.

The chamber environment is different for the two chambers available. A maximum pressure tolerance of 304 kPa for the larger rectangular chamber (and so no ability to use deeper treatment tables than the US Navy Treatment Table 6) meant 80% of recompressions were performed in the smaller cylindrical chamber, including 85% of all first treatments. All seizures occurred in the cylindrical chamber. The smaller chamber does not have space for an air-conditioning unit as used in the larger chamber, and swings in temperature and humidity occur with compression and decompression. A higher risk for seizure may be due to inadequate control of ambient temperature during operation. Alternatively, perhaps the smaller chamber size creates an enhanced sense of claustrophobia and anxiety in the diver, raising the risk of oxygen toxicity secondary to arousal of the sympathetic nervous system.

The medical indications for HBOT identified a patient-related effect on incidence of seizure. While dividing the medical indications into emergency and non-emergency groups was very much a rule-of-thumb process determined by the author, the group identified as emergency had a significantly higher risk of seizure. Fever, organ dysfunction and altered biochemistry might be considered causative factors although these claims are unsubstantiated. The hyperbaric physician might comment that the non-emergency group includes a number of conditions that would usually be treated at 243 kPa or even 203 kPa as opposed to 284 kPa (e.g., non-healing wounds and radiation tissue injury). This is true for current practice; however, clinical practice in the past has seen some of these conditions being treated at 284 kPa. Furthermore, treatment at 284 kPa has sometimes occurred as an operational requirement when time, space or staffing was limited.

In this study, carbon monoxide (CO) poisoning warrants mention with a risk of seizure found to be 0.6% of patients or 0.2% of treatments. These results are at odds with published studies that found the risk of seizure in HBOT treatment of CO poisoning to be about 3% of patients.[2,6] No explanation for this discrepancy can be suggested. Comparison with other published studies is difficult because most have reported oxygen toxicity over a range of treatment pressures between 203 and 304 kPa, with the majority around 243 kPa. The issue is further confounded by use of

multi-place versus mono-place chambers, oxygen delivery by mask versus hood, absence of a recognised uniform treatment profile and variable use of air breaks.

Apart from patient-related factors, three other influences on oxygen toxicity in the hyperbaric chamber are oxygen partial pressure, duration of exposure and use of air breaks. Experimental data have repeatedly related the risk of CNS toxicity to the absolute pressure of oxygen although much of this work has used oxygen partial pressures well in excess of those used clinically.[7] The overall incidence of seizure at 284 kPa from this study was 0.3%. Other studies that have utilised oxygen partial pressures of around 243 kPa have reported an incidence of seizure in the range of 0.03–0.06%,[8–10] an approximate tenfold reduction in risk, although most also involve what would be considered non-emergency indications. Hampson provides further clinical support in his report of 900 cases of CO poisoning treated at 248, 283 and 304 kPa.[2] Seizure was reported as significantly more frequent at higher pressures (0.3%, 3% and 2% of patients respectively).

Development of CNS toxicity has been linked to duration of exposure in many animal and human studies which have used a wide range of pressures and sometimes prolonged exposure times.[7] However, when examining clinical hyperbaric treatment with the pressure and duration of exposures typically used, no evidence could be found to support a predictable relationship between duration of exposure and seizure. Although the data in this study are incomplete, seizure does not appear to be related to duration of the treatment and can occur during the first or any subsequent period of oxygen treatment. The CO study by Hampson found no relationship between duration of the treatment and occurrence of seizure.[2]

The inability of clinical studies to clearly demonstrate increasing risk of seizure with increasing duration of exposure may be due to the deliberate use of oxygen pressures with a low risk for seizure, and the use of air breaks in treatment profiles. The use of air breaks is known to extend tolerance for pulmonary oxygen toxicity in humans;[7] however, their role in CNS toxicity is not so clear. Animal studies suggest a benefit from air breaks,[11] but the use of different animal species and different experimental endpoints does not support any predictable relationship between duration of exposure and CNS oxygen toxicity. Evidence for air breaks preventing CNS toxicity in clinical hyperbaric treatment is not available even though it is logical.

A clinical approach to controlling the risk of seizure due to CNS oxygen toxicity has usually invoked the use of a recognised treatment profile with a relatively safe oxygen partial pressure and duration of exposure. Additional factors are use of air breaks and an efficient oxygen delivery system, avoidance of fever, optimisation of biochemistry and minimisation of sympathetic nervous system activity, particularly in the emergency patient. Avoidance strategies and prompt recognition are all we have until the mechanism of CNS oxygen toxicity can be described.

On this front, it has been demonstrated that the cerebral vasoconstriction and reduced cerebral blood flow normally seen with hyperoxia can, at some point, be abolished resulting in cerebral blood flow that is actually increased above baseline.[12] The delivery of a large volume of hyperoxic blood, and subsequent reactive oxygen species, to certain excitatory areas of the brain may then lead to the EEG and clinical manifestations of oxygen toxicity. Nitric oxide appears to play a role in the initial vasoconstriction and in the subsequent cerebral vasodilatation, and may have other actions as well.[13,14] However, monitoring of cerebral blood flow and EEG does not appear to allow reliable prediction or termination of an impending seizure and cannot be recommended for routine clinical monitoring. Although made in reference to divers, the observation by Donald remains relevant to all chamber operators: that the susceptibility to seizure due to oxygen toxicity varies between individuals and within the same person on different days.[15]

Hyperbaric medicine professionals must therefore operate with the constant risk of oxygen toxicity. While symptoms of CNS oxygen toxicity can usually be managed easily by removal of oxygen, seizure is a more dramatic event. It poses a safety risk to the patient, the inside attendant and the other patients in the chamber, not to mention the distress such an event is likely to precipitate in them. Managed well it is known not to result in significant sequelae. Although prompt response to symptoms that may be due to CNS oxygen toxicity is vital, there is no guarantee that such a warning will be given. Clinical studies have clearly reported that a prodrome, or heralding sign of seizure, was not noticed in their experience.[8,10] An accurate understanding of the true incidence of CNS oxygen toxicity is vital to properly inform our patients and to guide us in providing the safest possible environment for treatment.

References

1 Davis J. Hyperbaric oxygen therapy. *J Intensive Care Med*. 1989; 4: 55-7.
2 Hampson NB, Simonson SG, Kramer CC, Piantadosi CA. Central nervous system oxygen toxicity during hyperbaric treatment of patients with carbon monoxide poisoning. *Undersea Hyperb Med*. 1996; 23: 215-9.
3 Smerz R. Incidence of oxygen toxicity during the treatment of dysbarism. *Undersea Hyperb Med*. 2004; 31: 199-202.
4 Smerz R. Gender disparity in incidence of oxygen toxicity during treatment for DCI. [Abstract] *Undersea Hyperb Med*. 2004; 31: 355-6.
5 Stephenson R, MacKenzie I, Watt SJ, Ross JA. Measurement of oxygen concentration in delivery systems used for hyperbaric oxygen therapy. *Undersea Hyperb Med*. 1996; 23: 185-8.
6 Sloan EP, Murphy DG, Hart R, Cooper MA, Turnbull T,

Barreca RS, et al. Complications and protocol considerations in carbon monoxide-poisoned patients who require hyperbaric oxygen therapy: report from a ten-year experience. *Ann Emerg Med*. 1989; 18: 629-34.
7 Clark J, Thom S. Oxygen under pressure. In: Brubakk A, Neuman T, editors. *Bennett and Elliott's physiology and medicine of diving*. London: Saunders; 2003. p. 358-418.
8 Welslau W, Ameling M. Incidence of oxygen intoxication of the central nervous system in hyperbaric oxygen therapy. In: Marroni A, Oriani G, Wattel F, editors. *International Joint Meeting on Hyperbaric and Underwater Medicine*; 1996 Sept 4-8; Milan, Italy. Bologna: Grafica Victoria; 1996. p. 211-6.
9 Hampson N, Atik D. Central nervous system oxygen toxicity during routine hyperbaric oxygen therapy. *Undersea Hyperb Med*. 2003; 30: 147-53.
10 Plafki C, Peters P, Almeling M, Welslau W, Busch R. Complications and side effects of hyperbaric oxygen therapy. *Aviat Space Environ Med*. 2000; 71: 119-24.
11 Clark JM. Extension of oxygen tolerance by interrupted exposure. *Undersea Hyperb Med*. 2004; 31: 195-8.
12 Chavko M, Braisted JC, Outsa NJ, Harabin AL. Role of cerebral blood flow in seizures from hyperbaric oxygen exposure. *Brain Res*. 1998; 791: 75-82.
13 Zhang J, Sam AD, Klitzman B, Piantadosi CA. Inhibition of nitric oxide synthase on brain oxygenation in anesthetized rats exposed to hyperbaric oxygen. *Undersea Hyperb Med*. 1995; 22: 377-82.
14 Demchenko IT, Boso AE, Whorton AR, Piantadosi CA. Nitric oxide production is enhanced in rat brain before oxygen-induced convulsions. *Brain Res*. 2001; 917: 253-61.
15 Donald K. *Oxygen and the diver*. Hanley-Swan: The SPA Ltd; 1992.

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