This quick reference guide is excerpted from Dr. Eric Kindwall's chapters "The Use of Drugs Under Pressure" and "Contraindications and Side Effects to Hyperbaric Oxygen Treatment" in *Hyperbaric Medicine Practice,* 3rd edition.

HYPERBARIC MEDICINE PRACTICE

3RD EDITION

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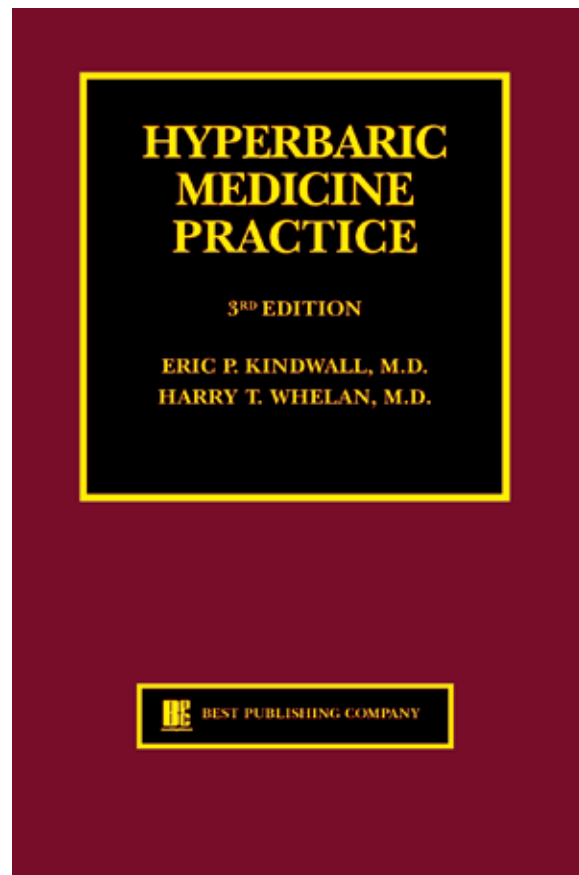
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DRUGS THAT POTENTIATE OXYGEN TOXICITY

Steroids

It is well known that the administration of adrenal corticosteroids can potentiate oxygen toxicity. There seems to be an increase in epinephrine and adrenocortical hormones in response to the stress of hyperbaric oxygen. Normally, the elaboration of these substances in response to stress serves as a protective mechanism. The reverse seems to be true in oxygen toxicity. Steroids and adrenaline seem to further sensitize the organism.[1]

In clinical practice, hyperbaricists are often called upon to treat people who are receiving steroids. It is a good idea to carefully watch the patient who is receiving high dose steroids and to give anticonvulsant drugs, prophylactically, if necessary. Frequent air breaks are often used. It has been our experience that patients on steroids may develop premonitory signs of oxygen toxicity more quickly than normal. Steroid mediated seizures have not been seen in patients exposed to U.S. Navy Tables 5 and 6, probably because of the short exposures to oxygen between air breaks.

We treated one patient with Addison's disease who was receiving maintenance steroids. Since in this patient the addition of the hyperbaric oxygen stress caused no further elaboration of adrenocortical hormones, the patient was not at any greater risk for oxygen toxicity, despite the fact that she was receiving exogenous steroid hormones.

Narcotic Analgesics

Be especially alert for oxygen toxicity in patients receiving morphine, meperidine (Demerol®) or one of the other narcotic analgesics. Narcotic drugs depress respiration by reducing the reactivity of the medulla to CO_2.[2-4] When the respiration is decreased, a rise occurs in the alveolar and arterial pCO_2. In addition, oxygen can have a depressant effect on respiration as well as a stimulatory effect. Oxygen leads to a further depression of ventilation in the presence of narcotic drugs. This exaggerated depression of ventilation leads to a still greater rise in arterial pCO_2 above normal.[5] The blood vessels of the brain dilate as a result of this increased pCO_2 and, because of the increased blood flow thus afforded, the amount of dissolved oxygen rises in brain tissue. The increased amount of oxygen in brain tissue speeds the development of oxygen convulsions. One should be particularly watchful if the patient has received one of these agents. Because intramuscular and subcutaneous absorption of morphine varies widely (although recent research shows the intramuscular absorption of drugs to be uninfluenced by HBO), the intravenous route is preferred for all hyperbaric patients. If the patient's respirations are noted to be slowed, the patient, if cooperative, should be instructed to take a number of deep breaths to blow down the CO_2 levels.

Central Vasodilator (Acetazolamide)

Acetazolamide (Diamox®) is a carbonic anhydrase inhibitor, which prevents oxygen-induced vasoconstriction. This is probably not a blocking mechanism, but it has an indirect

CO_2-related effect. Kong,[6] who provided photographic evidence of this effect in the retinal vessels, first demonstrated this. Its use has been described in the experimental hyperbaric treatment of sickle cell anemia.

The possible disadvantage is that by preventing systemic vasoconstriction it also permits greater cerebral blood flow during HBO treatment. This may predispose to CNS oxygen toxicity with seizures. The drug should probably not be used at chamber pressures greater than 2 ATA, and it might well be wise to consider prophylactic diazepam if the drug must be used at higher pressures. If a patient is already taking acetazolamide when referred for treatment there may be a higher risk of oxygen seizure at pressures greater than 2 ATA.

Its usefulness in the management of other hyperbarically treated conditions has not been studied or documented.

Thyroid (Synthroid®)

Iatrogenic production of hyperthyroidism with the administration of thyroid extract or thyroxin in experimental animals results in very pronounced enhancement of oxygen toxicity at atmospheric pressure and at increased ambient pressure. A thyroidectomy has the opposite effect. This has been demonstrated in animal studies, and one may reasonably assume that these factors would also be operative in human subjects selected for clinical exposure to hyperbaric oxygen. Presumably, this is due to the increased metabolic rate and its propensity to cause toxicity during exercise. Hypophysectomy also counters oxygen seizures. Active Graves' disease predisposes to seizures as the patient is hyperthyroid. There is no danger of oxygen toxicity in a patient taking thyroxin or Synthroid® to maintain a euthyroid state.

DRUGS THAT PROTECT AGAINST OXYGEN TOXICITY

Disulfiram (Antabuse®)

The use of disulfiram in blocking oxygen toxicity was tested by Faiman. He showed that mice could be exposed to 6 ATA, exercising for one hour, without convulsing, when pretreated with intraperitoneal disulfiram. Subsequent necropsy failed to demonstrate any CNS or pulmonary oxygen damage. This work was also repeated in beagle dogs at pressures of four atmospheres with little or no evidence of oxygen toxicity.[7] Hart (unpublished data) reported its use in one patient treated hyperbarically who had an extremely low seizure threshold. Hart's conclusion was that the effect is dose related. Dosage in the human has ranged between 500 mg and 300 mg per day. Obviously, anyone receiving disulfiram must not be using alcohol or have a recent history of ingesting alcohol. Alcohol swabs, mouthwash, and other sources of alcohol must be vigorously excluded from contact with the patient.

This medication is available for humans only in oral form and its efficacy in blocking seizures has not been demonstrated in a controlled trial with humans. Disulfiram probably acts in competition with enzymes containing SH bonds for the free radical oxygen and thereby exerts a protective effect.

The theoretical problem with using disulfiram in the chamber is that it also blocks the production of superoxide dismutase (SOD), which is the body's major protection against oxygen toxicity.[8] Based on the animal data, it was thought that disulfiram might pose a risk if taken in concert with HBO therapy.

It must be borne in mind, however, that the dosages of disulfiram given in the animal experiments were extremely high, corresponding to 14 grams of the drug given intraperitoneally in humans, and there have been no reports of a human having a problem with HBO while taking disulfiram. Therefore, it is no longer considered a contraindication.

Vitamin E (Alpha Tocopherol)

Research by Kann et al. and Okamoto et al. showed that alpha tocopherol deficient mice had a higher mortality in HBO.[9,10] Vitamin E also appears to protect against pulmonary oxygen toxicity. Poland, Bollinger, et al. have shown that vitamin E prolonged life in mice an average of 1.6 days compared to vitamin E deficient mice (4.9 vs. 3.3 days) when exposed to 100% oxygen.[11] The seizure threshold also appears to be raised by supplemental vitamin E. Hart recommends a dosage of 400 units p.o. per 90 minute treatment to be given at any time preceding treatment, allowing time for absorption (personal communication).

Phenothiazines

Of the phenothiazines, only chlorpromazine (Thorazine®, Largactil®) has been investigated with regard to its effect on oxygen toxicity. Bean et al. have demonstrated that chlorpromazine has a considerable protective action in the CNS against the seizure-producing propensity of oxygen under high pressure.[12] Again, it must be borne in mind that the absence of seizures does not necessarily mean absence of toxicity or the possibility of permanent damage if pressure/time limits are exceeded. This is interesting, as chlorpromazine, if given in large initial dose by itself, can produce convulsions. This is quite apart from its ability to produce a Parkinson-like syndrome. However, Bean felt that the protective action of the drug is due in large measure to the removal or blocking of neurogenic causal factors by a suppressant action on sympathetics at the hypothalamic and medullary levels as well as an anti-epinephrine effect. He demonstrates in the paper referenced that this protection is not due to chlorpromazine's hypotensive effect and a presumptive consequential decrease in cerebral blood flow and oxygen supply to the CNS. For this reason one would expect other phenothiazines, which do not affect vasomotor tone as much as chlorpromazine (such as the piperazine side-chain drugs), to have a similar effect. Suitable research in this regard is lacking, however. Chlorpromazine can safely be given in a dose of 50 mg intramuscularly initially and then 100 mg three times a day orally.

Of interest is that we have seen two patients who developed moderate to severe extra-pyramidal symptoms on minute or very moderate therapeutic doses of phenothiazines when associated with carbon monoxide poisoning. One patient taking Mellaril® 400 mg q.d.

developed extra-pyramidal symptoms and signs during hyperbaric treatment, and the other went into oculogyric crisis when given a tiny dose of phenothiazine (Stelazine® 2 mg) several days after apparent recovery from severe CO poisoning. This is presumed to be secondary to the damaging effects of CO on the basal ganglia. Both responded to IV diphenhydramine (Benadryl®).

FACTORS THAT PROTECT AGAINST OXYGEN TOXICITY
Hypothermia

Low body temperature (absent shivering) has long been recognized as a deterrent to oxygen toxicity, whereas an elevation of temperature has the opposite effect. The reason for this is believed to be largely due to the attendant changes in metabolism. Thus, the use of hypothermia in clinical procedures in HBO should diminish the possibility of oxygen poisoning as well as reduce oxygen consumption. This is true only if shivering is suppressed.

COMPLICATIONS AND SIDE EFFECTS
Seizures

Davis quoted the incidence of oxygen convulsions to be 1.3 per 10,000 patient treatments at a pressure of 2.4 ATA. In that series, air breaks of 5 minutes were given every 20 minutes.[13] These statistics were based on treatments given over a number of years at the hyperbaric laboratory of the United States Air Force School of Aerospace Medicine. In retrospect, it is now believed that a number of these patients who experienced seizures were hypoglycemic at the time and that they were probably seizures due to low blood sugar. If hypoglycemic seizures were excluded, the true incidence would be more like 0.7 seizures per 10,000 patient treatments. Today, clinical chambers may only give one air break in the middle of a 90-minute protocol. Some chambers use a 5-minute air break every 30 minutes.

Pulmonary Oxygen Toxicity

Oxygen can produce pulmonary toxicity at one atmosphere, but 24 hours of continuous oxygen breathing is usually required before early signs appear, such as substernal chest pain, dry cough, and a decrease in vital capacity. At 2 ATA, these changes appear within six hours of continuous exposure. However, continuous HBO exposures rarely exceed two hours clinically. In the treatment of decompression sickness on U.S. Navy Table 6, the patient breathes oxygen for four hours. Exposure time is interrupted for air breathing periods, during which time recovery from sub clinical toxicity takes place. Using the normal protocols published for HBO treatment, pulmonary oxygen toxicity has never been reported. If, however, the patient is continuously carried on FiO_2s greater than 40% between HBO treatments, toxicity of the lung may become a possibility.

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