# 9 Drug Interactions with Hyperbaric Oxygenation

K.K. Jain

Interactions of HBO with other drugs should be recognized for prevention of adverse reactions as well as for enhancement of therapeutic effects. This chapter looks at:

## Oxygen as a Drug

When oxygen is breathed in concentrations higher than those found in the atmospheric air, it is considered to be a drug. By this definition, hyperbaric oxygen (HBO) is definitely a drug and it can interact with other drugs. It is important to be aware of these interactions in patients who are receiving other drugs, for HBO can either potentiate or reduce the effects of other drugs. Conversely, there are also drugs that reduce or potentiate the effects of HBO. These correspond to protectors against and enhancers of oxygen toxicity, respectively, as discussed in Chapter 6.

Many drugs, including nonprescription drugs, have undesirable side effects that may be modified in the hyperbaric environment. Some drug effects are potentiated and some are antagonized; some agents produce entirely different effects than those observed in normobaric environments.

## Drugs Affecting the Central Nervous System (CNS)

**Anesthetics.** The interactions of anesthetics with HBO is discussed Chapter 38, but some of the drugs used are reviewed briefly here, due to their importance in many aspects of the current topic.

**CNS Stimulants.** CNS stimulants such as amphetamines interact unfavorably with HBO. And, notably, excessive coffee drinking in those who are susceptible to caffeine may also predispose to oxygen toxicity.

**Ethanol.** Hyperbaric air has a synergistic effect with ethanol and increases the sleeping time in mice. This may explain the increased susceptibility to the effects of compression and decompression of those who have imbibed alcohol. There are no special ill effects of HBO on patients who suffer carbon monoxide poisoning while they are inebriated. There is no evidence that HBO accelerates the metabolism of "sobering up" in alcoholics.

**Narcotic Analgesics.** Narcotic drugs generally depress respiration by reducing the reactivity of medullary centers to $CO_2$. This, combined with the depressing effect of HBO on respiration, can lead to a rise in $paCO_2$, which causes vasodilatation and enhances oxygen toxicity.

Pharmacokinetics of meperidine in dogs breathing air at 1 ATA is not altered under HBO at 2.8 ATA, or breathing air at 6 ATA. The findings in dogs cannot, of course, be extrapolated to humans, as the two species handle drugs very differently. The action of morphine also is unchanged by HBO.

**Pentobarbital.** It has been mentioned in Chapter 3 that pentobarbital anesthesia can be reversed in rats under atmospheric pressure. Attempts to distinguish between the two possible causes of this reversal – changes in the drug disposition and changes in drug-receptor interaction – by studying the pharmacokinetics of pentobarbital in dogs exposed to HBO shows no significant effect of HBO on total plasma clearance, volume of distribution, or elimination half-life of pentobarbital. This rules out changes in drug disposition as a cause of reversal of central nervous system (CNS) depression by pentobarbital.

**Scopolamine.** This is an anticholinergic compound used widely for management of motion sickness and may be used concomitantly with HBO, particularly in divers. Bitterman *et al* (1991) tested the interaction of scopolamine with HBO at 5 ATA in rats. The duration of the latent period preceding the onset of hyperoxic convulsions was not altered. However, the visual and cardiovascular side effects of the drug should be taken into consideration when scopolamine is used in combination with HBO.

## Interaction of HBO with Various Drugs

### Antimicrobials

HBO increases the permeability of the blood-brain barrier (BBB), as described in Chapter 2. This has led to the investigation of HBO as an enhancer of the penetration of some antibiotics across the BBB into the cerebrospinal fluid (CSF) in order to increase their effectiveness in meningitis.

**Aminoglycoside Antibiotics.** CSF transfer of the aminoglycoside antibiotic tobramycin is not altered under HBO in rabbits, and HBO has no significant effect on the CSF concentration of this agent. $CO_2$, which is known to damage BBB, more than doubles the CSF:blood ration for tobramycin. Pharmacokinetics of gentamicin does not change in healthy volunteers exposed to HBO.

**Sulfonamides.** Increase of oxygen tension has a synergistic bactericidal effect with sulfonamides rather than the usual bacteriostatic action. HBO and antibiotic synergism are discussed in Chapter 13.

Mafenide acetate (Sulfamylon), an antibacterial agent used in burn patients, is a carbonic anhydrase inhibitor and tends to promote $CO_2$ retention and vasodilatation. This substance must be removed from patients before they are placed in a hyperbaric chamber for HBO treatment.

### Antineoplastics

The role of HBO in enhancing cancer radiosensitivity is discussed in Chapter 36. Interaction of HBO with some antineoplastic agents will be described here.

Exposure of cancer cells to HBO at 3 ATA for 2 h produced inhibition of DNA synthesis or mitosis. Simultaneous exposure to HBO and adriamycin results in decreased cytotoxicity. However, exposure to adriamycin 2–8 h before or after HBO produces an increase in the drug effect. Cytotoxicity increases when cells were exposed to HBO before, during, or after nitrogen mustard administration.

HBO enhances the chemotherapeutic effect of doxorubicin both in cell culture and in the rat model (Petre *et al* 2003). HBO reduces the rate of misonidazole metabolism, thus increasing the concentration of this substance in tumors, which enhances radiosensitivity. However, doxorubicin is regarded as a contraindication for concomitant use with HBO therapy because of the increased risk of cardiotoxicity. An experimental study has shownb that HBO exposure does not potentiate doxorubicin-induced cardiotoxicity in rats, but confers cardioprotection against doxorubicin, which warrants further investigation (Karagoz *et al* 2008).

### Cardiovascular Drugs

**Adrenomimetic, Adrenolytic, and Ganglion-Blocking Agents.** Under HBO, there is a considerable reduction of hypotensive effect of α- and β-blockers, ganglion blockers, and b-adrenomimetics, and elimination of the effects of central adrenomimetics. The pressor effects of the directly and particularly of the indirectly acting a-adrenomimetics, as well as the cardiotropic effects of β-adrenoblockers, are potentiated. Therefore, these drugs should be given after but not before the HBO session.

**Digitalis/Digoxin.** HBO has been reported to decrease the effectiveness of cardiac glycosides. There is some evidence that HBO may reduce the toxic effects of digitalis.

**Antianginal drugs.** The effect of a single HBO session (1.5 ATA, duration 40 min), in combination with antianginal drugs, has been investigated in patients with ischemic heart disease and angina pectoris of effort, NYHA functional class II-III. HBO reduces the degree of indirect hemodynamic effect of nifedipine, potentiates negative chronotropic, and inotropic effects of propranolol – but has no impact on the degree of hemodynamic effect of depot-glycerol trinitrate.

**Heparin.** Heparin-treated animals exposed to HBO develop pulmonary hemorrhages as a result of interactions of the anticoagulant effect of heparin and oxygen-induced pulmonary lesions. The pressures and exposure times in experimental studies are much longer than those used clinically and these observations are not applicable to humans. However, since heparin has been used as an adjunctive measure in patients undergoing HBO treatments, this potential complication should be kept in mind, although none has been reported in patients on heparin undergoing HBO treatments.

### Interaction of HBO with Miscellaneous Drugs

**Insulin.** The dosages of insulin required in diabetes are decreased during HBO therapy and should be readjusted.

**Losartan.** Addition of HBO therapy to losartan, an angiotensin receptor blocker, increases the drug efficacy and has significant benefits in the management of proteinuria (Yilmaz *et al* 2006).

**Reserpine and Guanethidine.** Reserpine and guanethidine have been shown to interact unfavorably with HBO.

**Salicylates.** There is a significant increase in salicylate clearance in dogs at 2.8 ATA. There are no studies in humans.

**Theophylline.** There are no effects of HBO (2.8 ATA) on the pharmacokinetics of theophylline in the dog. There are no studies in humans.

## Practical Considerations of Drug Administration During HBO Therapy

The mechanical effect of the pressure on the drug containers should be taken into consideration. Drugs stocked in a multiplace chamber and subjected to repeated compression and decompression should be put into pressure-proof containers. There are no problems of explosion with small vials when pressures are below 3 ATA. Multidose rubber top vials should be used only once in a hyperbaric chamber because of possible contamination while withdrawing a drug. Precautions for intravenous infusions are discussed in Chapter 7.

## Drugs that Enhance Oxygen Toxicity

**Acetazolamide.** Acetazolamide is a carbonic anhydrase inhibitor that prevents oxygen-induced vasoconstriction and increases blood flow under HBO. This predisposes the

brain to the toxic action of oxygen. Acetazolamide should not be used at pressures greater than 2 ATA.

**CNS Stimulants.** See section on CNS drugs.

**Disulfiram.** This drug is used in alcohol aversion therapy. It may potentiate oxygen toxicity via *in vivo* reduction to diethyldithiocarbamate and subsequent inhibition of superoxide dismutase.

**Thyroid Extract.** Thyroid or thyroid extract given to experimental animals under HBO enhances the toxic effects of oxygen. The increase of metabolic rate is thought to predispose to oxygen-induced convulsions. It is a reasonable assumption that this would also occur in humans).

## Drugs that Protect Against Oxygen Toxicity

This topic has been discussed in Chapter 6 and a list of drugs that protect against oxygen toxicity is given in Table 6.6.

**Anticonvulsants.** Phenytoin (Dilantin) and diazepam (Valium) are used to prevent seizures, and do not have any protective effect against oxygen toxicity as such. Barbiturates are also used as antiepileptics, and may have a protective effect against oxygen toxicity. But the disadvantage of using barbiturates is that they are respiratory depressants. Diazepam (Valium) is used to prevent and control seizures of nonhyperbaric origin. The dosage is 5–50 mg given slowly by intravenous injection. It may also lead to respiratory depression. Lorazepam is similar in action to diazepam but requires one-fifth the dose. If phenytoin is used, care should be taken not to use high pressures of oxygen for long periods: CNS toxicity may occur without the warning signs of seizures. Carbamazepine has been found to be useful for the prevention of CNS toxicity during HBO therapy of epilepsy-prone patients.

**Ergot Derivatives.** Two ergot derivatives lisuride and quinpirole have been shown to antagonize convulsions in mice induced by HBO at 5 ATA. This protection was found to about 50% of that obtained by diazepam. There is no report of use of any ergot derivatives in patients for this purpose.

**Magnesium.** Mg ion compounds are substances with antioxidant and vasodilating effects and therefore reduce oxygen toxicity. A single dose of 10 mmol of magnesium sulfate can be given 3 h before a HBO session.

**Phenothiazines.** Chlorpromazine is considered to be protective against oxygen toxicity.

**Propranolol.** L-propranolol has been shown to protect mice against HBO-induced seizures (Levy *et al* 1976). There have been no reports of clinical application of this effect.

**Vitamin E.** Vitamin E is believed to protect against oxygen toxicity by counteracting the oxygen free radicals. A dose of 400 mg daily should be given to patients scheduled for HBO therapy starting 2 days before the therapy.

## Conclusions

Drug interactions with HBO represent an important subject, but there is a lack of studies for many of the commonly used medications. Animal studies cannot always be applied to humans. Therefore, studies of the pharmacokinetics of commonly used drugs in patients receiving HBO should be carried out and an authoritative drug incompatibility list compiled; such a list would be incorporated in various pharmacopoeias and displayed in hyperbaric treatment facilities. A careful history should be taken of drug use by patients and caution should be exercised in the use of drugs known to interact with oxygen.