Adjuvant drug therapy for decompression sickness: a review

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The primary treatment of decompression sickness is recompression and oxygen breathing at high pressure. This form of treatment has enjoyed a large measure of success in the past and continues to be essential. Recompression and high pressure oxygen breathing, however, do not always produce complete relief of symptoms. Failure to obtain complete relief is especially likely when the burden of omitted decompression is large and when there is a long delay in the institution of therapy. In cases where relief by recompression and oxygen breathing is likely to be incomplete, supplemental therapy with safe and effective drugs is very desirable. As knowledge of the pathogenesis of decompression sickness has advanced, an increasing number of drugs have been proposed as potentially useful therapeutic agents. This review examines the evidence for the safety and efficacy of these drugs. Emphasis is placed on those drugs used as adjuvants to relatively low pressure recompression therapy, i.e., 6 ATA or less. Interactions between drugs and the high pressure environment have been reviewed elsewhere (1) and are not considered here.

FLUID AND ELECTROLYTE THERAPY

In Type I decompression sickness (DCS) and in milder forms of Type II decompression sickness, serum electrolytes, hematocrit, and plasma volume remain unchanged or are altered only to a very mild degree (2–6). In extensive forms of the disease, however, a substantial loss in plasma volume and a concomitant rise in hematocrit have been observed both in human subjects (7–13) and in dogs (4, 6, 14–18). The loss of plasma volume appears to be primarily the result of an increase in vascular permeability (4, 6), although an elevation in central venous pressure may also play a role (16). Initially plasma is lost isotonically with respect to albumin (4). Ultimately, a loss of colloid osmotic pressure would be expected as vascular albumin continues to equilibrate with extracellular water.

A limited amount of data is available with regard to electrolyte changes in serious decompression sickness. Hypokalemia has been described in several cases (19). In one nearly fatal case, hyperkalemia and acidosis were observed (8). In general, case reports have not included electrolyte and osmolality data, and an animal study of these variables has not been reported to our knowledge.
Replacement of lost plasma volume is advocated to combat hypotension, restore organ blood flow, and reverse microcirculatory stasis. Recommended replacement solutions include dextran, plasma or denaturated circulatory equivalents, albumin solutions, and various crystalloid preparations (9, 20–25). Mannitol or other osmotically active agents are occasionally added to these regimens to reduce organ edema or enhance diuresis, or both (21, 22, 26, 27). Case reports have been published documenting a favorable outcome when plasma volume restoration with albumin and dextran-70 (9, 25) or plasma (10, 11) has accompanied recompression therapy. Fructus (28) reported a reduction in morbidity in Type II DCS prior to recompression when dextran was administered while the patient was en route to the chamber. In these and most other case studies several therapeutic interventions have been applied simultaneously, making it difficult, if not impossible, to assess the role played by plasma volume restoration alone.

Three experimental studies of fluid therapy in DCS have been reported. Wells et al. (29) and Childs et al. (30) observed that fluid replacement increases the velocity of blood flow through capillary beds in experimental decompression sickness. Cockett et al. (20, 31) noted in dogs that volume expansion with dextran (350–500 ml), whole blood (1 unit), and 5% glucose in water allowed 14 animals to survive a decompression that was uniformly fatal to control animals within 3–5 h post-exposure. Recompression therapy was deliberately withheld from both groups. The 14 treated animals were ambulatory within 12 h of leaving the chamber and remained normal for an extended period thereafter. In a subsequent experiment that was reported separately (25), 2 dogs were similarly exposed and treated with dextran-70. Both developed paraplegia 3–4 days after the acute episode of DCS. Histopathologic examination of the spinal cords revealed extensive destruction in both cases. Thus volume expansion alone would not appear to be adequate therapy despite the positive result reported for the 14 dogs earlier.

Dextran has perhaps been more widely used in the treatment of decompression sickness than any other specific fluid regimen (24, 28, 32). Two forms are in common clinical usage: dextran-40 has an average molecular weight of 40,000; and dextran-70, an average molecular weight of 70,000. Theoretical considerations and experimental evidence suggest that the volume expansion produced by dextran-40 is slightly greater than that produced by dextran-70, but of shorter duration because of rapid renal excretion of the polysaccharides of smaller molecular weight (30). In general, the difference in the volume-expanding properties of the two dextrans appears to be small (30).

Dextran-40 and dextran-70 have qualitatively similar effects on coagulation, which include the following: 1) decreased platelet adhesiveness and aggregation; 2) coating of platelets, erythrocytes, and endothelium; and 3) decrease in platelet factor 3 activity (33–36). These properties have been considered specifically useful in the restoration and maintenance of microcirculatory flow in DCS (37–40). To our knowledge only one experimental study of this premise has been conducted. Wells et al. (29) compared the capacities of Ringer’s Lactate and dextran for restoring microvascular perfusion of the dog during decompression sickness. No advantage of dextran over Ringer’s Lactate was noted.

Adverse effects of the dextrans include fluid overload, anaphylaxis, renal failure, and bleeding (36). Dextran administration also adds to the complexity of cross-matching blood for transfusion. Childs et al. (30) have pointed out that when the dextrans are given in proper dosages, the incidence of these adverse reactions is low. Indeed we know of no reported complications of the use of dextrans in DCS, including the patient reported by Norman et al. (41) whose therapy was complicated by gastrointestinal hemorrhage.

Elective isovolumetric hemodilution is a technique that can be used to lower blood viscosity by reducing hematocrit below normal values. Reduced vascular stasis and improved microcir-
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Summary

The current status of fluid replacement in severe DCS may be summarized as follows:

1. Replacement of lost plasma volume can be shown experimentally to be of benefit in the absence of recompression or other therapeutic interventions. The minimum extent to which restoration must proceed to achieve a beneficial effect (i.e., correction of hypotension only, return of hematocrit to normal, etc.) is unknown.

2. Case reports suggest that fluid replacement concomitant with recompression therapy or administered enroute to recompression therapy is also of benefit, but no controlled clinical or experimental trial has been conducted.

3. No advantage of using dextran-40 or dextran-70 over other forms of fluid replacement has yet been demonstrated.

4. The effects of mannitol and other osmotic agents are not well reported in case studies and in general these agents have been used where many other therapeutic interventions were proceeding simultaneously. No controlled clinical or experimental trial of these agents has been conducted.

5. Selection of the volume and the electrolyte, glucose, and colloid composition of replacement fluids remains a matter of judgment in individual cases. No data exist on the correction of specific ionic abnormalities in DCS or on the impact of the volume and composition of fluids on the development of organ edema (CNS, lung, etc.). In particular, the question of whether plasma volume deficits are better replaced by crystalloid or colloid solutions remains unresolved.

HEPARIN

Heparin is used clinically in high doses to produce full anticoagulation and in low doses to prevent venous thrombosis. Most studies of heparin in decompression sickness have used high doses, and the data from these studies are conflicting. Pertinent observations concerning high-dose therapy include the following:

Philp (42) studied heparin in a rat model of decompression sickness in which the animals were subjected to a dive and then decompressed to altitude shortly after surfacing. He reported a significant reduction in incidence and severity of bends when heparin in anticoagulant doses was given prior to the altitude ascent.

Inwood (43), using a similar rat model in which heparin was given prior to compression, could demonstrate no significant protective effect despite adequate anticoagulation.

Cockett et al. (44) reported that heparin without recompression, given 3 h after surfacing, was 100% effective in reducing mortality from decompression sickness in dogs. In this study experimental animals underwent arterial and venous catheterization whereas controls did not, and the period of observation and the neurological outcome of experimental animals were unspecified.

Reeves and Workman (45) studied heparin as adjunctive therapy for Type 1 decompression sickness in dogs. No benefit from heparin therapy was observed.

McCormick et al. (46) reported that prophylactic heparin significantly reduced hearing loss in guinea pigs with inner ear decompression sickness (20–80 dB loss in controls vs. 0–20 dB
loss in treated animals). In the same study McCormick also reported results from a small group of animals in which treatment with heparin in combination with urokinase resulted in temporary improvement in hearing loss.

Farmer et al. (47) have suggested that since hemorrhage may play an important role in the pathogenesis of inner ear decompression sickness, all anticoagulants should be withheld. Inner ear hemorrhage has been observed in both guinea pigs and squirrel monkeys following decompression (46, 48).

Laborit et al. (49) used a rabbit model of decompression sickness to study the effects of heparin in four conditions: 1) as an adjunct to recompression; 2) as first aid prior to recompression; 3) as a prophylactic agent; and 4) as a treatment without recompression. As these authors stated, the data suggested that heparin was beneficial as an adjunct to recompression and as a prophylaxis. Heparin appeared to be especially useful for prophylaxis and treatment of pulmonary symptoms of decompression sickness. Unfortunately, the numbers of animals used in this study were too small to permit a clear distinction between a heparin effect and the biological variability so characteristic of animal models of decompression sickness.

Two case reports have been published describing the use of heparin in anticoagulant doses for treatment of decompression sickness. In the case reported by Saumarez et al. (50) recompression therapy was not available. A number of drugs were used, including heparin and dextran. The patient presented 16 h after onset with visual disturbances, nystagmus, weakness and sensory loss of the right arm, and CO2 retention. Combined drug therapy was followed by significant improvement. Nystagmus was the sole residual deficit. A patient reported by Kindwall and Margolis (8) presented with hip pain and respiratory distress. Recompression therapy relieved only the hip pain. The patient’s respiratory status improved over several days of therapy that included intubation with mechanical ventilation, heparin, and many other therapeutic agents. In neither case was any adverse effect from heparin therapy described.

It is evident that the data and opinions concerning heparin therapy for decompression sickness are conflicting. Part of the discrepancy may be due to the use of different animal models. The timing of heparin administration may be another important variable. It is possible that heparin may be useful in some forms of decompression sickness. The evidence is not firmly convincing, however, and until more careful studies are done, heparin in anticoagulant doses cannot be considered to be of proved value in the treatment of this disorder.

The most important adverse effect of high-dose heparin is bleeding. If heparin were to cause hemorrhage into the spinal cord or the inner ear, irreversible neurologic deficits might result. At present, insufficient data exist to adequately assess the risk of this complication in the treatment of decompression sickness.

Low-dose heparin (10,000–15,000 U/day) is used clinically in postoperative patients and certain other groups of patients at high risk of venous thrombosis (51). Several case reports of low-dose heparin therapy in decompression sickness have been published. Barthelemy used heparin in doses of 50 to 100 mg twice daily for treatment of 1 case of air embolism and 4 cases of serious decompression sickness in human patients and stated, “we had spectacular improvements when other treatments had failed” (52). Clinical details of these cases were not specified. A patient reported by Miller et al. (53) was successfully treated with low-dose heparin as part of a regimen that also included dextran-70, dexamethasone, and saturation recompression. Landsberg (54) reported successful treatment of spinal cord DCS with a regimen which included low-dose heparin therapy plus repetitive oxygen treatment tables, steroids, and dextran-40 (54). In none of these case reports were any adverse effects described. Low-dose heparin therapy has not been studied systematically, however, and no conclusion concerning its efficacy in decompression sickness can be drawn at the present time.
COUMARIN ANTICOAGULANTS

Smith et al. (55) studied the effect of prophylactic warfarin on platelet and fibrinogen kinetics in miniature swine and found that warfarin did not prevent the immediate fall in platelet and fibrinogen survival times post-decompression. Prophylactic warfarin, however, did lead to earlier normalization of platelet survival (one week post-decompression in warfarin-treated animals vs. four weeks for control animals). The effect of warfarin on the clinical outcome of decompression sickness was not reported in that study.

Philip (42) and Inwood (43), in separate studies, tested prophylactic bis-hydroxycoumarin in the rat model of decompression sickness described above. Inwood gave the drug prior to compression. In Philip's study the drug was given after stage decompression to the surface but prior to ascent to altitude, as well as prior to compression. No significant benefit from the drug was seen in either study.

The usefulness of coumarin anticoagulants in the therapy of decompression sickness has not been investigated.

CORTICOSTEROIDS

Parenteral corticosteroids have been widely used as an adjunct to recompression with the intent of reducing brain and spinal cord edema. The rationale for this use is based on the positive experience with steroid therapy in other CNS disorders associated with vasogenic edema such as brain tumor and closed head trauma (56, 57). Steroids have also been given with the intent of delaying or preventing hypoxic cellular damage (41). Many case reports have documented a favorable outcome when parenteral steroids have accompanied recompression and other drug therapy in severe cases or those difficult to resolve. Unfortunately, no controlled clinical or experimental study of these drugs has yet been undertaken. Thus it is still not possible to make a definitive statement regarding the efficacy of parenteral steroids in severe DCS. Epidural or intrathecal steroid therapy also has not been studied.

The side effects of prolonged systemic steroid therapy are well known, but for short-term usage steroid therapy is relatively safe. Thus it does not seem unreasonable to administer systemic corticosteroids in cases of CNS decompression sickness.

ANTIPLATELET AGENTS

A number of studies have implicated platelets in the pathogenesis of decompression sickness (58). Because of this work, agents that alter platelet function have received increasing attention, primarily as a means of preventing decompression sickness. Most studies have either examined the effect of these drugs on postive platelet kinetics or assessed their value as prophylactic agents against decompression sickness. The role of antiplatelet agents in the treatment of decompression sickness remains largely undefined.

Effects of drugs on platelet kinetics post-decompression

The effects of prophylactic aspirin on postive platelet kinetics in human beings have been reported in two studies by Philip and co-workers (59, 60). No definite changes in platelet levels or platelet survival times were noted.
Prophylactic dipyridamole was reported to have no significant effect on platelet kinetics in humans following decompression (60), but the dipyridamole analogues VK 744 and RA 233 were said to retard post-decompression falls in circulating platelet levels (59, 61).

Studies of the effect of dipyridamole and aspirin in combination on postdive platelet kinetics in both humans and miniature swine have been reported (55). In miniature swine prophylactic use of these agents did not prevent a postdive fall in platelet survival time. Continued treatment with these agents, however, led to normalization of platelet survival after 1 week compared to 4 weeks for untreated animals. In one group of animals, withdrawal of the agents after 1 week led to a second fall in platelet survival time. These results suggested that in miniature swine the stimulus for platelet consumption continued for 4 weeks post-decompression, but that platelet consumption itself was moderated by dipyridamole and aspirin in combination.

In humans, prophylactic dipyridamole and aspirin moderated but did not eliminate the immediate postdive fall in platelet survival time (mean platelet survival time with dipyridamole and aspirin 7.3 ± 0.4 days vs. 5.2 ± 0.5 days without) (55).

The effect on platelet kinetics of an anticoagulant (heparin or Coumadin) plus dipyridamole and aspirin has also been examined in miniature swine (55). The combination of these agents completely prevented postdive platelet and fibrinogen consumption. Preliminary studies reported in abstract form by the same group suggest that the same combination of antithrombotic agents may facilitate the development of diving-related osteonecrosis (62).

**Antiplatelet drugs as prophylaxis against decompression sickness**

A number of antiplatelet drugs have been found to have no value for prophylaxis when tested in rat models of decompression sickness. Included in this category are dipyridamole (63) and hydroxyethylrutoside, oxypentifylline, and sulphipyrazole (64).

Prophylactic studies of aspirin in the rat have produced conflicting results. Inwood (43) and Bennett and Brock (65) gave aspirin 1–2 h prior to compression-decompression. In the study reported by Inwood, the doses of aspirin were sufficient to inhibit platelet aggregation in response to ADP and collagen. Both studies failed to find any beneficial prophylactic effect. Popovic et al. (66) gave aspirin daily for 30 days prior to a compression-decompression stress and found a significant reduction in both morbidity and mortality.

Aspirin in combination with codeine was given to humans prior to ascent to altitude and did not decrease either the incidence or the severity of the resultant decompression sickness when compared to a placebo (67).

Two other antiplatelet drugs have been reported to have prophylactic value against decompression sickness. The dipyridamole analogue VK 774, given prophylactically, decreased morbidity and mortality from decompression sickness in rats (43). The drug nicergoline, which is said to interfere with platelet aggregation and to produce peripheral vasodilatation, has also been tested in the rat (68). Decreased mortality and decreased post-decompression falls in circulating platelet levels were reported in the treatment group.

**Antiplatelet drugs as a treatment of decompression sickness**

Broussolle et al. (69) reported on the use of an experimental antiaggregating agent (2574SE) in the treatment of decompression sickness in mice. Decreased mortality was seen in the treated group. The numbers of animals tested were too small to permit statistical analysis of the data.
Aspirin has been specifically recommended as an adjuvant to recompression therapy (38). No controlled clinical or experimental trial of this drug in the treatment of DCS has yet been conducted.

Summary

To summarize the data on antiplatelet agents:

1. Studies suggest that several single antiplatelet agents and the combination of aspirin and dipyridamole, when administered prophylactically, are capable of modifying platelet kinetics following decompression. When used singly, neither aspirin nor dipyridamole appears to possess this property.

2. A number of studies in animal models have shown that certain antiplatelet agents are capable of ameliorating the decompression syndrome when administered prophylactically. Dipyridamole is not in this category. A beneficial effect for aspirin is seen only with chronic administration. The extent to which antiplatelet agents may be useful as prophylaxis against decompression sickness in humans remains to be established.

3. Unconfirmed data in animals suggest that combinations of anticoagulants and antiplatelet agents may be associated with an increased risk of aseptic bone necrosis. The magnitude of this risk, and the spectrum of drugs with which it may be associated, requires further assessment.

4. There are essentially no controlled studies in which antiplatelet agents have been used as a treatment for decompression sickness. As a consequence, the safety and efficacy of antiplatelet drugs for this purpose has not been established.

DIAZEPAM

Diazepam is considered a standard part of the therapeutic regimen of decompression sickness by several sectors of the commercial diving industry. Cox (70) cites more than 70 instances in which the drug has been used. Anticipated beneficial effects include sedation, an increased threshold for CNS oxygen toxicity, and a lessening of the vertigo, nausea, and vomiting when inner ear involvement is present.

The anticonvulsant properties of diazepam are well known. Two groups have examined the anticonvulsant properties of diazepam against HBO-induced seizures in the mouse and reported their findings as abstracts (71, 72). Both groups found that diazepam was protective in these circumstances.

Farmer et al. (47) specifically recommend diazepam for the control of symptoms of labyrinthe decompression sickness on the basis of its beneficial effects in other vestibular disorders. Control of symptoms would be particularly desirable if repeated vomiting prevents wearing an oxygen mask. It must be noted, however, that a controlled trial of diazepam in inner ear decompression sickness has not been reported in the open literature. In the one case of vertigo bends cited by Farmer et al. (47) in which diazepam was used, recovery was coincident with recompression.

Kindwall (21) specifically recommends against the use of diazepam in vestibular bends because of the potential loss of symptoms as a therapeutic guide to the efficacy of recompression.
BRONCHODILATORS

A few studies concerning the prophylactic use of bronchodilators in decompression sickness have been reported. Baldin and Liner (73) reported that terbutaline, a β-2 agonist, administered before the dive, decreased the incidence of bends in rabbits. Sykes (64) studied the effect of prophylactic salbutamol on the effectiveness of recompression therapy for decompression sickness in the rat. No benefit was observed. Campbell and Spencer (74) reported that nebulized theophylline administered prophylactically decreased the incidence of decompression sickness in guinea pigs. In another study, theophylline was given orally to human volunteers prior to the induction of altitude decompression sickness (67). No beneficial prophylactic effects were noted.

Only a limited amount of data concerning the therapeutic need for bronchodilators in DCS is available. Increased airway resistance has been reported in dogs following pulmonary air embolism (75), but the role of airway resistance changes in the pathogenesis of DCS has not been studied experimentally. Bronchospasm does not appear to be a common clinical occurrence in decompression sickness. A few cases have been reported in which patients with DCS exhibited wheezing and impaired gas exchange. In the case reported by Saumarez et al. (50) the arterial blood gases improved after treatment with aminophylline. The patient described by Kindwall and Margolis (8) had diffuse rales, rhonchi, and wheezing in association with arterial hypoxemia and hypercapnia. Therapy with aminophylline did not seem to improve the respiratory abnormalities in this patient. No adverse effects of aminophylline therapy were reported in either of these patients.

A potential adverse effect of bronchodilators in decompression sickness is facilitation of transpulmonic passage of gas bubbles from the venous to the arterial side of the systemic circulation. Butler and Hills (76) have reported that, in the dog, aminophylline administered before the insult facilitated transpulmonic passage of microbubbles injected into the right ventricle. Furthermore, transpulmonic passage of the bubbles into the arterial circulation was associated with significant physiological alterations that included systemic hypotension and T-wave changes in the electrocardiogram. These results suggest that the use of bronchodilator drugs in patients with decompression sickness could be hazardous. Further work is needed to establish both the safety and the efficacy of these agents.

ANTIARRHYTHMIC DRUGS

Kizer (5) recently published a case report in which lidocaine was used as an adjunct to recompression therapy. The patient had neurological decompression sickness and frequent premature ventricular contractions, the etiology of which could not be established. Treatment consisted of recompression following U.S. Navy Table 6 and continuous lidocaine infusion at rates up to 4 mg/min. Recovery from ventricular ectopy was coincident with recompression. No adverse effects of lidocaine therapy were noted.

VASODILATORS

Vasodilators (e.g. nitroglycerin and nitroprusside) have been proposed as possible adjuvant therapy for decompression sickness (77). This class of drug has not been studied experimentally.
VASOPRESSORS

Hypotension unresponsive to recompression and intravenous fluid therapy clearly indicates the need for therapy with vaspressors. Agents which might be considered include isoproterenol, epinephrine, norepinephrine, phenylephrine, ephedrine, and dopamine. Unfortunately, none of these drugs have been studied experimentally as an adjunct to the treatment of decompression sickness.

OTHER AGENTS

Indomethacin has been evaluated as a prophylaxis against decompression sickness in the rat by Inwood (43), who could not demonstrate a beneficial effect. In the dog however, Wells et al. (15) found that prophylactic indomethacin lessened plasma volume loss during experimental decompression sickness. The mechanism of the effect was believed by the authors to be an interference with prostaglandin production.

Hilton and Wells (78) have shown that prophylactic nicotinic acid (a total dose of 22.5 mg/kg) is also capable of retarding plasma volume loss during experimental decompression sickness in the dog. The mechanism of this effect is unknown. The authors postulate that the drug may act by decreasing the available supply of fatty acid precursors to prostaglandin synthesis.

Novotny (79) has administered nicotinic acid (100 mg) orally, three times daily, in two patients with decompression-induced hearing loss. In both cases, hearing returned to pre-injury levels within 2–3 weeks. As the author has clearly stated, these case reports do not permit distinction between drug effect and spontaneous recovery.

Prophylactic value against decompression sickness was found for chlorpromazine (80), and Pluronic F-68 (43) in rats, and for amidopyrine in obese mice (81). The phenothiazine derivative, dimethothiazine, has been found to have prophylactic value in studies using obese mice (82) and dogs (83).

Recently, cyproheptadine, given either alone (84) or in combination with amphetamine (85) has been shown to have prophylactic value against decompression sickness in mice. Cyproheptadine alone was not useful as a treatment of decompression sickness (84).

In a study by Popovic et al. (66) prophylactic levodopa was shown to reduce the incidence and severity of decompression sickness in the rat. Levodopa appeared to act synergistically with aspirin in this regard in that prophylactic administration of both drugs resulted in a greater reduction of morbidity and mortality than either drug given alone. In a separate study from the same group, therapeutic levodopa facilitated recovery from paraplegia induced by air embolism in the rat (86).

Although many of these results are promising, at the present time the data are inadequate to justify routine use of these drugs in the treatment of patients with decompression sickness.

COMBINED THERAPY

Recently, Fructus (28) reported the results of a retrospective study of drug therapy administered enroute to the recompression chamber. Sixty-seven cases of neurological decompression sickness were cited. Fourteen patients received no adjuvant therapy before recompression, 3 received oxygen alone, 5 received oxygen plus intravenous aspirin, and 45 received a combination of oxygen, intravenous aspirin, corticosteroids, and low-molecular-weight dextran. The delay from the onset of decompression sickness to the institution of recompression
therapy ranged from 3 to 24 h, with a mean delay of 10 h. Of the 53 patients who received some form of adjuvant therapy, 12 were asymptomatic upon arrival at the chamber and were not recompressed, 26 were improved, and 15 were unchanged. Of the 14 patients not receiving adjuvant therapy, none demonstrated any improvement during transport to the chamber. These results strongly suggest that some form of drug therapy during transport to the chamber is beneficial, particularly where a delay in recompression therapy is anticipated. Firm conclusions cannot be drawn from these data as presented, however, since the type and severity of the insult and the magnitude of the time delay before recompression are not specified for the treated and untreated groups. In addition, it is not possible to define the individual role of the 4 drugs tested.

CONCLUDING REMARKS

The accepted method for determining the safety and efficacy of a drug is the prospective randomized and controlled double-blind study in patients with the disease in question. The foregoing review emphasizes that no drug or combination of drugs has ever been shown by this method to be safe and effective for adjuvant therapy of decompression sickness. Due to the infrequent and scattered occurrences of decompression sickness, it is unreasonable to expect that such trials will be soon forthcoming.

In the absence of controlled human trials, we believe that choices of drugs for therapy of decompression sickness can be justified in several ways:

Knowledge of the pathogenesis of decompression sickness strongly recommends certain agents. A clear example of this basis for decision making is the use of fluid therapy to combat hemoconcentration.

A second basis for drug selection involves the application of a drug in decompression sickness based on the known effects of the drug in other disorders that may have similar pathogenetic mechanisms. Since this rationale for drug selection is not directly supported by experimental evidence, it is especially important to consider the potential harmful effects of the drug. An example of drugs often chosen in this manner is the group of corticosteroids. The experience with steroid therapy in the treatment of other CNS disorders suggests a potential for reducing brain and spinal cord damage in decompression sickness. Given the severity of these problems, this potential benefit would appear to outweigh the known complications of short-term steroid therapy.

The most important basis for drug selection is the clinical presentation of the patient. While no particular drugs have been proved effective in decompression sickness, neither have any been shown to be absolutely contraindicated. There is, therefore, no reason to withhold standard measures for the treatment of serious medical problems, such as bronchospasm, hypoxia, or hypotension, if the clinical evaluation suggests that these conditions pose a serious threat to the patient with decompression sickness.

We do not suggest that there are new principles for drug selection in the treatment of DCS. On the contrary, these are the principles that are regularly applied in the field, and they represent, in our opinion, the state of the art of drug therapy for this disorder.

Several other points may be made:

Although much important work has been done on the use of drugs for the prevention or treatment of decompression sickness, more research is needed. It appears that as in the past, future studies will need to use animal models of the disease.

Most studies to date have examined the value of various drugs as prophylaxis against decompression sickness. While this type of study is very important in its own regard, usefulness
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of an agent for prophylaxis does not necessarily imply usefulness of the same agent for treatment. More controlled animal trials are needed in which drugs are assessed as a treatment of decompression sickness.

Many of the currently available drug studies have focused on the effect of a drug on some phenomenon associated with decompression, e.g., platelet consumption. The fact that a drug can reverse some such phenomenon does not mean that the same drug will improve the clinical outcome.

Due to the complexities of the derangements in decompression sickness, it seems likely that species differences may be an important determinant of drug effects. Promising drugs should be tested in more than one species, especially when the ratio of therapeutic dose to toxic dose appears to be small.

Very few studies actually have assessed drugs as adjuvants to recompression and high pressure oxygen breathing. It is entirely conceivable that high pressure oxygen may alter the effects of a drug. Such alterations might include decreases in effectiveness, alteration in pharmacokinetics, or enhancement of toxicity. Studies that assess drugs as adjuvants to high pressure oxygen and use clinical outcome as an end point should allow discovery of unfavorable interactions between drugs and high pressure oxygen.

Anecdotal reports do not constitute a suitable substitute for controlled clinical trials. Nevertheless, it would be useful to have a central registry to which case reports of human decompression sickness could be reported for compilation and distribution. While such case reports cannot be used to prove the efficacy of a given drug, they might help identify drugs that appear particularly useful or particularly dangerous. These drugs could then be subjected to careful testing in animals.

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