ADJUVANT THERAPY FOR DECOMPRESSION ILLNESS

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Accidents, decompression illness, drugs, treatment.

Current Knowledge

The definitive treatment of DCI is administration of oxygen in a recompression chamber. However, in recreational diving a chamber is rarely available on site, often necessitating delays of several hours before recompression can be initiated. This is potentially a "golden period" during which simple measures may make a significant difference in outcome.

Surface (First Aid) oxygen

In severe DCI, which can be complicated by aspiration of water or vomitus, administration of oxygen is a standard first aid measure to reverse hypoxaemia and enhance oxygen delivery to under-perfused tissue. Additionally, when breathing 100% oxygen, the partial pressure gradient for diffusion of inert gas from bubble into tissue ("oxygen window") is increased. This has been observed in experimental animal preparations.[1,2] The effectiveness of oxygen administration to injured divers is supported by clinical experience. Analysis of 2,192 recreational diving accidents reported to the Divers Alert Network revealed that 68% of divers who received surface oxygen reported partial or complete resolution of symptoms before recompression versus only 40% who had no supplemental oxygen.

Blood glucose control

Both brain[3] and spinal cord[4] injury can be worsened by hyperglycaemia. The most likely mechanism is accelerated production of lactate producing intracellular acidosis. The effect appears to become significant above a threshold plasma glucose of around 200 mg/dl (11 mM).[5,6] Administration of even small amounts of glucose, for example one litre of intravenous 5% dextrose solution, even in the absence of significant hyperglycaemia, may worsen neurological outcome.[7] Therefore, unless treatment of hypoglycaemia is required, it is best not to administer glucose containing intravenous solutions. If there is reason to suspect hyperglycaemia (e.g. if high dose corticosteroids are prescribed) plasma glucose should be measured, if feasible, and appropriate treatment initiated.

Fluids

Interaction of bubbles with vascular endothelium causes a capillary leak resulting in loss of plasma volume. Haemoconcentration, often of severe degree, has been reported in DCI,[8-11] and post-treatment residual symptoms have been correlated with the degree of haemoconcentration (see Table 1). Fluid administration can replenish intravascular volume and reverse haemoconcentration, thereby increasing tissue perfusion.[8]

Indirect evidence suggests that aggressive hydration during minor surgical procedures can result in more rapid elimination of anaesthetics,[12] from which one might infer that a similar approach in divers with decompression illness may accelerate the washout of excess inert gas. It has been demonstrated that augmentation of central blood volume and cardiac preload using supine position,[13] head down tilt[14] and head out immersion[13,14] significantly increase the rate of inert gas washout. Therefore, fluid administration may be advantageous, even in patients with DCI who are not dehydrated.

Rapid intravenous administration of hypotonic fluids can cause CNS oedema,[15] whereas administration of fluids which are hypo-oncotic but not hypo-osmolar has no effect on CNS water. There is therefore no advantage of colloidal solutions over crystalloids,[16,17] and any isotonic IV fluid without glucose, such as normal saline or Ringer's solution, will suffice. Theoretical objections have been raised to the use of fluids containing lactate (e.g. Ringer's lactate or Hartmann's solution) on the grounds that liver metabolism may be reduced, especially if the patient is hypothermic, and that lactic acidosis can result. However, lactate is metabolised by most tissues, not only by the liver, and the small amounts of lactate in Ringer's lactate solution are unlikely to contribute significantly to acidosis.

TABLE 1

HAEMATOCRIT IN DIVERS WITH DCI AND IN CONTROLS (from Boussuges et al)[11]

		Haematocrit (%)		
	Number	**Median**	**Minimum**	**Maximum**
Controls	16	42.5	39.0	48.0
DCI without neurolgical sequelae	39	42.0	35.0	57.0
DCI with neurological sequelae	19	47.5	32.0	69.5

IV administration of fluid is the most rapid method of rehydration and for critically ill patients it is generally agreed that IV administration is preferable to the oral route. However, there is disagreement about whether there is any advantage to parenteral fluid administration for divers with less severe disease, particularly for divers with pain as the only symptom. In dehydration due to other clinical situations, such as cholera, moderately severe dehydration can be satisfactorily treated using appropriate oral fluids.[18] Therefore, it is argued that many divers with DCI, provided they are alert and not nauseated or vomiting and sufficient volumes of fluid can be ingested without undue interruption of oxygen administration, can be satisfactorily rehydrated orally.

Ingestion of plain water stimulates urine output via a decrease in plasma osmolality and inhibition of antidiuretic hormone (ADH) secretion, producing a false impression of adequate rehydration.[19,20] Therefore a solution containing electrolytes, particularly sodium, is preferable. Maximum water absorption occurs at a sodium concentration of 60 mM and glucose concentration in the range of 80-120 mM. Gastric emptying rate may be reduced by protein or glucose concentrations greater than 5% (252 mOsm/kg). An ideal solution for rehydration in diarrhoea has been suggested as containing approximately 30-60 mM sodium, 70-150 mM glucose and osmolality of around 240 mOsm/kg,[21,22] a mix attained by few commercially available beverages, which are usually low in sodium and high in carbohydrate (see Table 2).

The rate at which rehydration can be achieved after mild dehydration in normal volunteers have revealed mixed results. In one study dehydration of 4% of body weight (12% reduction in plasma volume) was induced by exposure to a hot, dry environment.[19] Administration over four hours of fluid equal to the volume lost, using either demineralised water or glucose-electrolyte solution (sodium 22 mM, osmolality 444 mOsm/kg), failed to normalise plasma volume, although urine output had increased to 180-380 ml/hour. Even after an additional 24 hours of ad lib fluid intake plasma volumes were 2.4-5.5% below pre-test values. On the other hand, in a study of dehydration induced by exercise plasma volume was restored within 20 minutes by ingesting water with sodium chloride (sodium concentration 77 mM) but not until one hour using a sucrose solution.[20]

A palatable oral rehydration fluid with appropriate electrolyte and carbohydrate concentration can be improvised by mixing one part orange or apple juice with two parts water and adding 1 teaspoon of salt to one litre of the mixture. If salt is not available, the appropriate sodium concentration can be achieved by diluting the juice with a mixture of one part sea water and 9 parts fresh water.[23]

Provided that the patient is not vomiting, an intake of 1,000-2,000 ml per hour is safe and tolerable. End points for fluid therapy should include normal haemodynamics and haematocrit. Urine output should exceed 1 ml/kg per hour, bearing in mind that if large volumes of hypotonic fluids

TABLE 2

COMPOSITION OF BEVERAGES

Beverage	Sodium (mM)	Potassium (mM)	Glucose (mM)	Osmolality (mOsm/kg)
Ideal replacement	30-60		70-150	240
Water	0	0	0	0
Apple juice	7.8	19.1	784	730
Club soda	9.7	0.5	0	20
Coca Cola Classic™	1.8	0.0	628	750
Diet Coke™	1.0	1.4	5	10
Gatorade™	23.0	3.0	256	330
Ginger Ale	3.2	0.4	527	535
Orange juice	14.5	28.2	708	793
Powerade™	10.7	3.4	471	499
Snapple™ Kiwi Strawberry	0.0	-	818	818
Sprite™	6.0	0.0	595	607
Beer	2.0	8.0		600
Pedialyte™ (Ross)	45.0	20.0	139	269
Rehydralyte™ (Ross)	75.0	20.0	139	329
WHO-Oral Rehydration Solution	90.0	20.0	167	387

are used, the urine output may be elevated out of proportion to the rehydration. However, fluid should not be withheld just because an ideal liquid is not available.

If fluids are not available rehydration can be simulated by immersion to the neck in water, which redistributes 500-800 ml of blood from the extremities to the thorax, increasing cardiac output. Provided that the diver can be kept warm, head out immersion, although impractical during transport, enhances inert gas washout.[13]

Corticosteroids

Use of pharmacological doses of glucocorticoids to treat neurological DCI has had variable results. In a retrospective review of arterial gas embolism (AGE) Pearson and Goad reported that after initial improvement secondary deterioration occurred less often in divers who had received glucocorticoids.[24] However, glucocorticoids have not been shown to be beneficial in the treatment of head injury,[25-27] or in animal models of decompression illness.[28] In a series of AGE cases analysed retrospectively for a possible relationship between glucocorticoid administration and outcome, no benefit was evident.[29] However, in traumatic spinal cord injury there is evidence that early administration (within 8 hours after injury) of methylprednisolone (30 mg/kg intravenously over one hour followed by 5.4 mg/kg/hour for 23 hours) can improve outcome six months after injury.[30] Such high doses have not yet been specifically tested in DCI, either in animals or humans. Moreover, the only systematic animal studies have used only short term outcomes, with somatosensory evoked responses as the end point, a measurement which, in humans, correlates poorly with clinical neurological function. There are currently no published data providing unequivocal support for the use of corticosteroids in DCI, although the evidence to the contrary may only be due to the lack of a trial using an appropriate dose. Therefore, the issue of efficacy of these compounds in this disease remains an open question.

Lignocaine

In models of AGE in both cats[31] and dogs,[32] lignocaine administration designed to achieve standard clinical plasma drug levels has improved short term neurological outcome. Randomised trials of lignocaine in humans have not yet been reported, although anecdotal reports support its use in DCI.[33,34]

Safe intravenous administration of lignocaine requires an infusion pump and the capability of dealing with untoward effects such as seizures. Early experience with intramuscular administration in the "field" for arrhythmia prophylaxis in acute myocardial infarction suggests IM injection is a safe method of administration of this drug to divers with DCI immediately after the onset of symptoms.[35] Injection of 200-400 mg into the deltoid muscle results in therapeutic plasma concentrations for up to two hours. Routine recommendation of such a regimen would require demonstration of benefit in an appropriately designed trial.

Anticoagulants

Because of the potential for bubble-blood interactions to cause platelet deposition and vascular occlusion refractory to recompression, it has been speculated that inhibitors of platelet function and soluble clotting factors might offer some benefit in DCI. In asymptomatic divers administration of aspirin and other anti-platelet drugs reduces the mild drop in platelets observed after routine dives.[36,37] A single case report of heparin administration to a patient with neurological bends indicated neither benefit nor harm.[38] However, animal studies in which single agents were administered have shown no benefit of anticoagulants, except for one study,[39] in which only a triple combination of indomethacin, PGI_2 and heparin resulted in a beneficial short term effect in a canine model of AGE.

Histological evidence of haemorrhage has been described in arterial gas embolism,[40] inner ear decompression sickness[41] and spinal cord decompression sickness,[42-45] suggesting that antiplatelet drugs or other anticoagulants may actually worsen outcome in DCI. However, in individuals with severe neurological bends and leg weakness, deep vein thrombosis (DVT) and fatal pulmonary thromboembolism have been described.[46] Therefore in these patients some form of prophylaxis against DVT, which may include low dose heparin or low molecular weight heparin,[47] is recommended.

The analgesic effects of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) prescribed for the discomfort of pain-only bends may render it difficult to assess the clinical response to recompression.

Body temperature

Animal models of CNS injury have demonstrated that outcome is significantly worsened by hyperthermia.[48] So fever in a patient with DCI should be vigorously treated.

Whether hypothermia may be beneficial has been an open question. In a recently published study of closed head injury (Glasgow Coma Scale 3-7), the effect of induced hypothermia on outcome was examined in 82 patients.[49] Forty patients were in the experimental group and were cooled to 33°C using cooling blankets and chilled nasogastric lavage fluid. Minimum body temperature was achieved on average 10 hours after injury. The patients were kept at 32-33°C for 24 hours then rewarmed. All patients

were mechanically ventilated during the experimental period. Twelve months after injury, 62% of the patients in the hypothermia group and 38% of those in the normothermia group had good outcomes (Glasgow Outcome Score of 4 or 5: moderate, mild, or no disabilities). For patients with severe neurological DCI active cooling might be a modality worthy of investigation.

Future developments

Pressure and oxygen remain the mainstays of treatment for DCI. However, there are relatively few degrees of freedom in the choice of ambient pressure, time of treatment and PO_2. Unless there is a major advance in the prevention of oxygen toxicity it is unlikely that any new treatment tables will offer major therapeutic advantages over current implementations. I believe that the next major improvement in DCI treatment will be in pharmacotherapy.

Fluorocarbons

Both oxygen and inert gases are highly soluble in fluorocarbons. Thus, intravenous administration of these agents in doses sufficient to increase the transport of these gases in plasma should simultaneously increase tissue oxygen delivery as well as accelerate insert gas washout. Animal studies have in fact demonstrated a reduction in mortality in gas embolism.[50,51] Perfluorocarbons may become available for clinical use in other settings, which would facilitate human studies in DCI.

Adjunctive agents

Prolonged anoxia due to interruption of blood supply can produce rapid cell death due to depletion of intracellular energy sources. Reperfusion of ischaemic brain before cell death has occurred can result in rapid recovery of cellular respiration and ATP synthesis and return of electrical activity. However, increased production of oxygen free radicals can lead to neuronal death due to ischaemia-reperfusion and death delayed many days (apoptosis). Understanding of the mechanisms underlying these events may lead to the development of compounds which may improve outcome after DCI. These concepts have been reviewed by Warner.[52]

After CNS injury there is a release of excitatory neurotransmitters such as glutamate, which then facilitates the entry of calcium, which is neurotoxic, into cells.[53] Blockade of voltage-dependent calcium channels by nimodipine and nicardipine has been shown to ameliorate somewhat the damage due to subarachnoid haemorrhage and ischaemic stroke,[54] but to have little effect upon outcome after global ischaemia induced by cardiac arrest.[55]

Calcium entry into cells can also occur with activation of specific glutamate receptors, such as N-methyl-D-aspartate (NMDA), a-amino-3-hydoxy-5-methyl-4-isoxazole propionate (AMPA) and 1-aminocyclopentyl-trans-1,3-dicarboxylic acid (t-ACPD). After an ischaemic insult, blockade of these receptors might conceivably reduce entry of calcium into the cell, thus preserving neuronal function. NMDA receptor blockers can protect against focal insults,[56] and AMPA receptor blockers protect against both focal and global injury.[57-62]

Compounds related to the corticosteroids, but without many of the side effects of corticosteroids ("lazaroids"), have been tested in subarachnoid haemorrhage with both positive[63] and negative[64] results.

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