ADJUVANT THERAPY OF DECOMPRESSION SICKNESS

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Introduction

The primary treatment of decompression sickness remains recompression and the breathing of elevated partial pressures of oxygen. It is important to treat as soon as symptoms arise and even before signs present. The latency of onset of neurological (CNS) decompression sickness (DCS) shows a relation between rapid speed of onset, severity and possible poor outcome of treatment in both humans and animals. This may be explained by an autochthonous mechanism. Initial recompression will improve ischaemic damage due to bubble formation which may cause slower onset of DCS. It will not improve damage due to tissue destruction caused by bubble nucleation and compression from autochthonous gas.[1,2]

If gas bubbles form in the epidural venous plexuses in animal experiments they can block all flow through spinal capillaries causing spinal cord anoxia.[3] Bubbles provoke activation of the clotting mechanism which causes further damage. Recompression will not immediately reverse these changes and additional measures will be needed.

Recompression will reduce the bubble size, or volume of tissue gas, allowing restoration of microcirculatory flow and may reduce secondary compression effects, in tissue, of an expanding volume of gas. It will also tend to drive the gas back into solution for elimination via the lungs. The gradient can further be improved for denitrogenation by breathing oxygen. Swindle observed reduced blood sludging as soon as the partial pressure of oxygen was increased.[4] It further stabilises the capillary endothelial lining and tends to reduce oedema by its vasoconstrictive effect on arterioles.

There are cases on record to show the effect of delay in therapy.[5] The pathophysiology of all forms of decompression sickness is still not fully understood but it is known that other systems are affected such as the clotting mechanism and complement activation. The systemic effects of tissue damage and shock are caused secondarily to the primary event of the generation of a critical volume of gas in the tissues, which can migrate into the circulation by the mechanical effects of bubbles, pressing on blood vessels causing ischaemia, and on nerves, causing neuropraxia, as well as tissue damage due to the expanding bubbles, and by interactions at the bubble-blood interface.

Large changes in plasma volume occur as capillary permeability is increased by the consequences of tissue damage and activation of the clotting system also. Not all cases of decompression sickness respond to recompression and oxygen therapy and on rare occasions a paradoxical response is seen. We have seen such cases at the North Sea Medical Centre.[6] Some cases appear to be so severe that they just will not respond and the pathology has been investigated.[7] There is a continuing need to examine adjunctive methods of treatment, intravenous fluids and drugs.

Fluid and Electrolyte Therapy

In serious (Type II) DCS, loss of plasma volume, and rise in haematocrit occur[8] due to increased vascular permeability and there is also a rise in central venous pressure (CVP) and pulmonary arterial pressure (PAP).[9] A fall in platelet count and electrolyte disturbances such as hypokalaemia occur.[10] Hypotension may occur and intravenous fluids are needed to reverse this to replace losses due to microcirculatory changes.

Kindwall stressed the importance of adequate early hydration, both orally if appropriate and intravenously, to prevent venous stasis.[11] He aimed at a urine output of 1-2 ml per kilogram per hour. Plasma colloid and crystalloid solutions have both been used. There was a particular vogue for the use of dextrans, but caution has been advised in the use of colloid volume substitutes whilst justifying their use clinically.[12] However in 1985 the Committee on Safety of Medicines issued a warning of adverse reaction reporting 55 cases of anaphylaxis with dextrans over the years including 10 deaths. The FDA (Federal Drug Administration) in the USA reported 12 adverse reactions and 3 deaths in the first half of 1983 to both dextran 40 and dextran 70. In the three fatalities in this series, less than 10 ml had been infused.

Fructus reported considerable improvement in delayed cases given dextran en route to the chamber.[13] Childs reported that incidence of side effects was low with dextran if it was used in the proper dosage with adequate crystalloid.[14] However Drugs and Therapeutic Bulletin again warned of anaphylactive reactions (mild in 1 in 2,000 infusions and severe in 1 in 6,000 infusions) in 1987.[15]

More recently pre-treatment with hapten injection "Promit" is said to have virtually eliminated this risk by binding circulating antibodies to dextran.[16] Dextran 70 inhibits platelet aggregation and renders fibrin more susceptible to fibrinolytic enzymes thus helping to prevent venous thrombosis. Infusion of more than 20 ml per kilogram (1,500 ml for 70 kilograms) can reduce Factor VIII levels mimicking the effects of von Willebrand's disease. So this is not the best choice as a plasma substitute where large volumes may be needed. It may also interfere with cross matching should blood transfusions be necessary for any reason.

Wells has shown in animals that any compatible intravenous crystalloid will reverse the circulatory effects of severe decompression sickness and is much more beneficial if used in conjunction with recompression.[17]

In the first instance, if the patient is conscious, oral fluids (isotonic or slightly hypertonic) should be given. Otherwise intravenous infusion of Ringer's Lactate or 4% dextrose in 0.18% saline or normal saline should be given. The U.S. Navy warns against introduction of too much lactate.

Colloid infusions (albumin) have been given when colloid osmotic pressure has dropped below 19-20 mm of mercury. In view of the extravasation of fluid it would appear, at first sight, superior to simple volume replacement. However albumin is widely distributed in the extravascular space across even normal capillary membranes. This may promote fluid retention.[18] Increased interstitial fluid in the lung will hinder oxygenation and elimination of nitrogen. Cockett showed that in experimental decompression sickness in dogs, those treated with volume expansion with dextran, whole blood and 5% glucose in water, survived severe decompression sickness whereas controls did not.[19] In another experiment, 2 dogs were similarly exposed, treated with dextran 70 alone, and both developed paraplegia subsequently. Histological examination of the spinal cord revealed extensive tissue destruction. Thus, plasma volume expansion alone is not adequate, despite a successful intravenous régime devised by Saumarez in 1973 to treat a case of neurological DCS in Guernsey, before a recompression chamber was available there.[20]

Drugs

Attempts to stabilise the capillary endothelium using prostaglandin inhibitors or NSAIDs such as indomethacin have been made.[17] Plasma volume loss of 20% or more has been described in human dysbarism.[21] Vasoactive substances play a part. Bradykinin is involved as are other kinins, histamine and serotonin, in addition to prostaglandins (in later stages). Thus, prostaglandin inhibitors significantly, but not completely, reduce the plasma volume loss in the first hour after decompression in pretreated animals.[17] This means that other mechanisms are at work.

STEROIDS

These stabilise capillary endothelium and were initially thought to have an anti-oedema effect. Initial fears of exacerbation of CNS oxygen toxicity were not borne out in the U.S. Navy. However, they take some time to become effective. Initially the oedema is vasogenic but after a time becomes cytotoxic when steroids are ineffective. They may play a part in preventing secondary oedema in cerebral arterial gas embolism (CAGE). The recommended dose is 500 mg-1 g of rapidly acting steroid (hydrocortisone hemisuccinate) i.v. as a bolus with 8-12 mg dexamethasone i.m.. The dexamethasone is repeated 6 hourly for 2 to 3 days.

Dexamethasone was evaluated in the treatment of acute spinal cord DCS.[22] In anti-inflammatory doses it did not appear to influence the outcome in that animal model.

Glucocortocoids have a number of actions which might modify some of the pathogenesis of spinal cord DCS but the delay of onset of the anti-inflammatory effect is too slow. More rapidly acting non-steroid anti-inflammatory agents (NSAIDs) may be more beneficial[22]. Theoretically "megadose" steroids (dexamethasone 15 mg kg^{-1} or methylprednisolone 30 mg kg^{-1}) may improve damaged spinal cord and blood flow, reduce superoxide-induced damage or improve the conduction of impulses by the spinal cord. However pulsed doses of dexamethasone or methylprednisolone have caused several sudden deaths.[23] In experimental animals methylprednisolone was not shown to be of benefit in treatment of acute spinal cord DCS.[24] The early histology of spinal cord DCS is not inflammatory but consists of derangement of myelin, punctate haemorrhages and perivascular oedema. Ischaemia is also an early feature. Based on his two animal studies Francis,[22,24] concluded that administration of corticosteroids to humans with spinal cord DCS is at present difficult to justify.

CEREBRAL OEDEMA

50% solution of glycerol in water (0.8 ml per kg) is said to be superior to mannitol and urea, the maximal effect occurring in 1 hour and not causing rebound oedema. However, it does cause intense nausea. It can be given by nasogastric tube.[24]

ASPIRIN

This inhibits platelet aggregation (2 x 300 mg given initially) and exerts the maximal effect in 30 minutes and is useful in prophylaxis but is not effective in therapy unless given before exposure.[25]

NARCOTIC ANALGESICS

Severe agitation, restlessness or convulsions mean diazepam may have to be given, again with the problems of masking symptoms. Diazepam must be used with caution to treat severe vestibular neuronitis in conjunction with recompression.[26]

HEPARIN

Catron in a review[25] quotes from Cockett who showed that heparinised dogs subjected to decompression insult did survive whereas control dogs did not.[27] Philp had produced similar conclusions from experiments in obese rats.[28] Saumarez successfully treated a diver with intravenous fluids, steroids, oxygen and heparin when recompression was not available.[20] The lipaemia clearing property rather than anticoagulant effect of heparin is thought to be responsible. Reeves and Workman did not find benefit after DCS in dogs.[29] The dose is similar to that used in the prophylaxis of venous thrombosis (2,500-3,000 units i.v. every 8 hours).

Anticoagulants are definitely contra-indicated in vestibular DCS because haemorrhage has been found in inner ear DCS.[26] Cerebral haemorrhage has been described after experimental air embolism in dogs and haemorrhages have been described in animal spinal cord decompression

sickness. Therefore anticoagulants are not now recommended.

COUMARIN ANTICOAGULANTS

Smith studied the effect of prophylactic Warfarin on platelet and fibrinogen kinetics in immature swine and found Warfarin did not prevent the fall in platelets and fibrinogen survival time post decompression.[30] Philp[28] and Inwood[31] tested bisdydroxycoumarin in separate studies in the rat after decompression followed by an altitude excursion. Inwood[31] gave the drug at the initial compression and Philp[28] prior to the altitude excursion without significant benefit.

ANTIPLATELET AGENTS

These have not been defined or assessed.

Combined Therapy

Retrospective case reports strongly suggest the benefit of oxygen, aspirin (1,000 mg) and dextran.[13] However, no prospective randomised controlled double blind trial in patients with decompression sickness has been performed.

In the absence of these trials drugs which are useful elsewhere in medicine may be used.

Standard first aid and resuscitative procedures should be carried out. Bronchospasm, hypoxia and hypotension should be treated. Intravenous aminophylline should be used with caution because this may release bubbles trapped in the lung filter on to the arterial side of the circulation.[32]

It must be remembered that hyperbaric oxygen may alter the effect of drugs under pressure and modify some of their actions.

Conclusions

Even after first aid treatment has been given and even if there is complete spontaneous resolution prior to recompression, nevertheless, recompression is advised.

At the North Sea Medical Centre the preferred treatment for serious DCS, particularly with any delay in recompression, would be:-

1 100% oxygen by tightly fitting mask.
2 Oral fluids if conscious and passing urine.
3 I.V. fluids - normal saline, dextrose-saline or any compatible crystalloid. Dextran 70 would be used for treatment in the immediate phase of life threatening DCS, using hapten pre-injection, however this injection must be given before any colloid leak develops.
4 Hydrocortisone 200-300 mg I.M. stat with dexamethasone 12 mg stat and 4 mg I.M. t.d.s. for 5 doses. This would particularly be used if CAGE were a possibility.

More recently there has been a report of benefit in treating patients with spinal cord injury with large dose methyl prednisolone[33] (a bolus of 30 mg kg^{-1} followed by 5.4 mg kg^{-1} per hour for 23 hours).

This has provoked further consideration of the use of steroids although the underlying pathology differs from decompression sickness.

None of this should prevent, or slow down, transfer to a suitable double lock chamber for urgent recompression.

A combined multi-system approach must be used in severe decompression sickness and further methods continue to be evaluated. As the differing pathologies of DCS are elucidated treatment may be tailored accordingly, for example to time and mode of onset.

There is evidence that latency of onset of DCS is a prognostic indicator. If a large prospective human study were to confirm this then a comparison of human and animal treatment régimes could be made.[2]

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