ORIGINAL ARTICLES

THE ROLE OF LIGNOCAINE IN THE TREATMENT OF DECOMPRESSION ILLNESS A REVIEW OF THE LITERATURE

Simon J Mitchell

Introduction

Decompression illness (DCI) is a complex multisystem disease of diving and aviation, for which definitive treatment comprises compression and administration of hyperbaric oxygen (HBO). Recent studies reveal an undesirably high failure rate for current treatment protocols and indicate the need for alternatives and/or effective adjuvants to HBO. In vivo data suggest a role for lignocaine (lidocaine) in the treatment of DCI, and possible mechanisms of action in this role have been identified. This paper briefly reviews the pathophysiology and treatment of DCI and, in the context of this discussion, examines the evidence suggesting a role for lignocaine as an adjuvant to HBO. Several studies of lignocaine in the treatment of DCI or analogous pathologies are currently under way.

Pathophysiology of decompression illness

Decompression illness arises secondary to the formation of bubbles outside normal gas containing spaces (intracorporeal bubbles) following reduction of ambient pressure.[1] Intravascular[2-4] and extravascular[5-7] bubbles may arise from inert gases dissolved in the blood or tissue respectively. Intravascular bubbles may also arise from pulmonary barotrauma.[8-10]

Intravascular bubbles may: obstruct blood vessels causing tissue ischaemia,[11] disrupt endothelium,[12,13] and activate leucocytes[14-16] platelets,[14,17,18] and biochemical pathways such as the complement[19,20] and kinin[1] systems. Secondary microcirculatory compromise and tissue ischaemia may follow due to clotting,[17,18] intravascular volume loss with red cell sludging,[21,22] increase in interstitial fluid pressure,[1] and leucocyte aggregation.[23] Extravascular bubbles may mechanically disrupt both surrounding tissue[1] and blood flow through adjacent microvessels.[24,25] Secondary activation of leucocytes and inflammatory pathways may also follow extravascular bubble formation.[7] Intra- or extravascular leucocyte activation may cause tissue damage through cytotoxic substance release.[26,27] In summary, intravascular and extravascular bubbles may give rise to tissue damage which may be ischaemic, mechanical, or inflammatory in nature.

Multiple organ systems may be compromised by these processes,[28] however the most dramatic and potentially debilitating consequences of intracorporeal bubble formation are observed when the central nervous system is affected. Aspects of bubble induced ischaemic and inflammatory damage to neurones are particularly relevant to the subsequent discussion of lignocaine.

Cerebral arterial gas embolism (CAGE) may cause neuronal ischaemia in two phases. Occupation of a vessel by a bubble may cause a period of complete ischaemia, which is relieved by redistribution of the bubble into the venous circulation,[29,30] with restoration of flow. Subsequently, there may be a more protracted period of relative ischaemia as perfusion is reduced by secondary inflammatory changes, particularly the accumulation of leucocytes on damaged endothelium.[31,32]

Neuronal ischaemia leads to loss of energy substrate for membrane ion pump function and a consequent disabling of intracellular homeostasis.[33] There is efflux of potassium and influx of sodium leading to loss of excitability (and therefore function), opening of voltage dependent calcium channels, and release of excitatory amino acids. The resultant increase in intracellular calcium, which is enhanced by opening of agonist operated membrane channels and calcium sequestration from intracellular sources, enables a complicated cascade of injurious reactions, involving protein kinase C and calmodulin, and ultimately leads to cell death.

Treatment of decompression illness

First aid management of DCI includes resuscitation, horizontal positioning of the victim, and administration of 100% oxygen (FIO_2=1) and fluids.[34] Recompression and HBO are the major components of definitive DCI treatment.[35] Compression reduces bubble size in accordance with Boyle's Law, thus encouraging the redistribution of intravascular bubbles and relieving the mechanical distortion of tissues by extravascular bubbles. Hyperbaric oxygen administration increases the diffusion gradient for nitrogen between bubble and lungs, thus achieving more rapid bubble resolution and elimination of nitrogen from tissue.[35] Hyperbaric oxygen may also have a role in reducing the accumulation of leucocytes in response to tissue and vessel damage or hypoxia.[36]

Since approximately 3 bar is the greatest oxygen tension that may be breathed in treatment before the incidence of convulsions becomes unacceptably high, modern treatments are most often based on compression to the equivalent of 18 m of sea water (2.8 bar) breathing 100% oxygen,[35] the "minimal recompression oxygen

tables". Animal data do not suggest any advantage for deeper compressions on air or modified oxygen-nitrogen mixtures.[37,38] However the recently described advantages of helium oxygen (heliox) mixtures over oxygen in tissue air bubble resolution,[39,40] have raised the possibility of more effective deeper treatments using heliox, unencumbered by risk of convulsion. Evaluation of heliox tables versus the minimal recompression oxygen tables in DCI treatment is currently underway.[41]

Administration of intravenous fluids to ameliorate the microcirculatory compromise which follows intravascular volume loss, clotting, and leucocyte accumulation, is the only adjunctive therapy to compression which is firmly recommended.[35] Although widespread, the administration of corticosteroids in DCI is controversial and largely unsupported by convincing data.[42] There is some in vivo data to support the use of indomethacin, prostaglandin I_2 and heparin in combination in DCI,[43] but in vivo haemorrhagic complications have been widely reported and this therapy is not recommended.[35]

Recent post-recompression follow-up surveys of several groups of DCI patients consisting mainly of recreational divers, suggest that failure rates for current treatment protocols are unacceptably high,[44-47] with residual cognitive changes being prominent. It follows that therapeutic recompression strategies more effective than the minimal recompression oxygen tables are being tested, and that effective cerebroprotective adjuvants to recompression are sought.[48] One potential adjuvant is lignocaine and the evidence in support of this is discussed below.

The role for lignocaine in treatment of DCI

Lignocaine is a cationic amide compound which blocks membrane sodium channels. It has a high volume of distribution, readily crosses the blood brain barrier,[49] and is rapidly metabolised by the liver with the metabolites undergoing renal excretion.[50] In sufficient concentrations, lignocaine can prevent the propagation of action potentials along excitable membranes. It is used as an injectable or topical local anaesthetic, and as an injectable antiarrhythmic agent (class lB) in the prophylaxis of ventricular tachycardia and fibrillation.[50] Lignocaine has a relatively low therapeutic index,[50] and a therapeutic range for antiarrhythmia treatment of 6-21 μmol/l. Plasma levels are monitored to prevent toxicity which may be manifest as cerebral irritability, bradycardia, atrioventricular (A-V) block, or myocardial depression.[50] Lignocaine should not be administered to patients with a supraventricular arrhythmia or heart block.

In vivo data indicate a protective role for lignocaine in ischaemic cerebral injury and other central nervous system insults. Much of this data relate to experiments in injuries analogous to DCI. A number of experiments have been reported which provide possible mechanistic explanations for lignocaine's protective effect. Key functional protection and mechanistic studies are described below.

Preservation of neural function during ischaemia by lignocaine.

Early in vivo studies of CAGE pathophysiology revealed that such events caused severe cardiac arrhythmias, acute hypertension,[51] severe elevation of intracranial pressure (ICP) and significant increases in plasma catecholamines.[52] It was also observed that lignocaine eliminated or significantly attenuated these changes.[52,53] It was proposed that these beneficial effects might translate into protection of cerebral function, and the first experiment specifically investigating cerebral function preservation by lignocaine in CAGE was reported by Evans et al.[54,55] Anaesthetised cats were pretreated with 5 mg/kg lignocaine in a short infusion five minutes before a single bolus of 0.4 ml of air was injected into the vertebral artery. Mean sciatic/cerebral somatosensory evoked response (SER) in an untreated control group initially fell to 28% of baseline value, recovering to 60% and 73% over one and two hours respectively. The mean SER in the treatment group initially fell to 68% of baseline, recovering to 89% and 95% over one and two hours ($P<0.01$ for all differences). Lignocaine also attenuated the increases in heart rate, blood pressure, and ICP seen in the control group.

The same authors subsequently published another study using a modified model, and administration of lignocaine after the injury.[56,57] Cats received 0.08 ml increments of air into the carotid artery until the SER was reduced to 10% of baseline levels over a period of 5 minutes. Five minutes later, treatment group cats received lignocaine in a 1.5 mg/kg bolus, followed by an infusion at 3 mg/kg over 30 minutes, then 1 mg/kg every 30 minutes thereafter. This regimen was demonstrated to achieve plasma levels of 8-16 μmol/l for the duration of the experiment. Control and treatment group mean SER recovered to 32.6% and 77.3% of baseline respectively over 100 minutes ($P= 0.001$). In an important additional experiment lignocaine alone was found to have no effect on the SER of uninjured cats.

In another CAGE experiment, Dutka et al. produced cerebral dysfunction in anaesthetised dogs using a single bolus of 0.4 ml air to the carotid artery, and a pharmacologically induced post embolic hypertensive spike.[58,59] Animals were not entered into the study unless the embolus reduced SER to ≤10% of baseline. Control and treatment group animals received HBO treatment with a modified USN Table 6A,[60] while treatment animals also received a post-injury lignocaine infusion using the same

dosage regimen used by Evans et al.[57] On completion of the Table 6A, the mean treatment group SER had recovered to 60% baseline versus 32% for the control group (P< 0.01). Average post-injury cerebral blood flow (CBF) was significantly greater in the lignocaine treated group (P=0.019). This study was important in the specific context of DCI therapeutics since a role for lignocaine as an adjuvant to HBO was indicated. Limited anecdotal human data support this contention. Drewry and Gorman reported a case of neurological DCI, refractory to HBO, in which dramatic improvement seemed temporally related to lignocaine therapy.[61]

These CAGE experiments generated interest in lignocaine as a cerebroprotective agent in other forms of ischaemic injury. While the studies performed in this area are not directly related to DCI, the emergent role for lignocaine in brain protection is of relevance.

Gelb et al. describe a feline model of severe focal cerebral ischaemia (middle cerebral artery occlusion for six hours) in which a 5 mg/kg bolus of lignocaine produced a transient protective effect as indicated by preservation of SER compared with controls.[62,63]

Sutherland et al. administered a 5 mg/kg bolus of lignocaine to a treatment group of rats 10 minutes before a 10 minute period of incomplete global ischaemia (achieved by bilateral carotid artery clamping and artificially induced hypotension).[64] A saline control group received a bolus of saline equivalent in volume to the lignocaine dose, and an untreated control group received neither lignocaine nor saline. Rats were allowed to recover for seven days after ischaemia before being sacrificed for cerebral histopathology. In lignocaine treated rats there was significantly less neuronal injury in the CA3 region of the hippocampus (P <0.05 compared with untreated controls). A numerical trend towards less severe grades of injury was recorded in other areas in the lignocaine treated rats, but this was not significant.

Shokunbi et al. administered a bolus and infusion of lignocaine to a treatment group of cats 30 minutes before and then throughout three hours of middle cerebral artery occlusion and three hours of reperfusion with SER monitoring.[65] Their dose regimen achieved plasma levels which peaked at 20.63 μmol/l after the bolus and 30 minutes of the infusion, falling to 12.85 μmol/l after two hours of reperfusion. A control group received a bolus and infusion of saline equivalent in volume to the lignocaine dose. Treatment group mean SER was better preserved at induction of ischaemia, and recovered to higher levels compared with controls (P <0.05). Histopathological analysis post mortem revealed mean infarct size (cross sectional area of a standardised section) to be significantly smaller in the treatment group (P <0.05).

In a complex series of experiments using rabbits, Rasool et al. administered an infusion of lignocaine at 0.2 mg/kg/min for 15 minutes, before, throughout, and for 40 minutes following a 20 minute period of incomplete global ischaemia titrated to produce standard EEG changes.[66] The amplitudes of both the positive and negative peak potentials of the SER decreased significantly less during ischaemia, and recovered more quickly and significantly more completely during reperfusion in the treatment group compared with a control group.

Nagao et al. administered a 3 mg/kg bolus of lignocaine followed by a 2 mg/kg/hr infusion beginning immediately before, and throughout, 12 hours of left cerebral hemisphere exposure to air achieved by craniotomy and dural resection.[67] This model precipitates progressive cerebral oedema and ischaemia. In the lignocaine treated animals there was significant preservation of SER latency duration, preservation of direct cortical response amplitude in the cortex and white matter, preservation of cerebral blood flow, and reduced oedema in the cortex, compared with controls.

Several investigations of lignocaine in cerebral ischaemia have failed to demonstrate any protective effect.[68,69] Shokunbi et al. administered lignocaine to cats in unconventional doses (50 mg followed by 50 mg/kg/hr) to produce and maintain EEG flattening, beginning 30 minutes before, and continuing throughout left middle cerebral artery clamping for four to six hours.[68] Histopathological brain examination at the end of the ischaemic period revealed no difference in the size of the grossly infarcted area between treated and control cats. The extent of the severe neuronal alteration was reduced in the treated group but this was not significant.

Warner et al. administered lignocaine in unconventional bolus doses (mean 23.5 mg/kg), titrated to produce a pre-epileptogenic EEG pattern in rats, immediately before 10 minutes of global ischaemia.[69] There was no significant difference between treatment rats and a control group with regard to post ischaemic EEG recovery, brain water content at 90 minutes post-ischaemia, or histopathological changes at seven days post-ischaemia.

McDermott et al. administered lignocaine to cats concurrent with compression and HBO therapy beginning 15 minutes after air embolism to the carotid artery (0.08 ml increments sufficient to reduce the SER to <10% of baseline for 15 minutes).[70] The dose regimen used by Evans et al.[57] was employed. The lignocaine with HBO group exhibited a significant improvement in SER recovery compared with a group receiving no treatment at all, but was not significantly different from a group receiving HBO alone. No lignocaine only group was tested, so this result may simply reflect salvage of the same population of compromised neurones by HBO and lignocaine, with no additive effect.

Several authors report investigations of lignocaine protection in spinal injuries.[71,72] Kobrine et al. administered lignocaine using the Evans regimen[57] to cats, beginning 15 minutes after a 15 second balloon catheter inflation in the T6 epidural space.[71] There was significant return of the sciatic SER of three of five treated cats, compared with minimal return in only one of five controls. Moreover, there was markedly less haemorrhagic damage on histopathological examination in the cords of treated cats. In a similar experiment using a weight drop method to inflict the injury, no recovery occurred in either group.[72] However, the weight drop spinal injury may be too severe to allow a realistic possibility of neuronal recovery with any treatment.[73]

In summary, lignocaine administered both prophylactically and immediately after injury, in doses designed to achieve plasma levels comparable to conventional antiarrhythmic levels in humans, has been demonstrated to be protective of cerebral function in a number of animal models of air embolism, focal ischaemia, and global ischaemia.[54-59,62-67] It has failed to provide protection when administered in doses achieving plasma levels greater than conventional antiarrhythmic levels, and in relatively severe models of focal and global ischaemia.[68,69] There is conflict regarding its additive effect to HBO in the treatment of air embolism,[58,59,70] and regarding its role in the treatment of spinal injury.[71-73] The key features of the cerebral protection studies are summarised in Table 1.

Mechanisms of protection

The four possible mechanisms commonly proposed to explain the neuroprotective properties of lignocaine are respectively titled: the neuronal membrane stabilisation / ion channel blockade hypothesis; the reduction of the cerebral metabolic rate of oxygen ($CMRO_2$) hypothesis; the haemodynamic modification hypothesis; and the modification of leucocyte and other blood element activity hypothesis. The evidence supporting each of these theories is discussed below.

THE MEMBRANE STABILISATION / ION CHANNEL BLOCKADE HYPOTHESIS

From the earlier discussion of ischaemic neuronal injury mechanisms,[29] it can be reasoned that a delay or deceleration of ischaemic ion shifts might protect neurones. The protective effect of hypothermia in cerebral ischaemia[74] is now universally accepted and it has been demonstrated that in ischaemic cortical neurones hypothermia both decreases the depletion of adenosine triphosphate (ATP)[75] and delays ischaemic ion shifts.[76] It is unclear whether a pharmacologically induced reduction in ischaemic ion shifts would also equate with protection.[77] Nevertheless, Astrup et al. found that lignocaine in extremely high doses (160 mg/kg) significantly delayed cortical potassium efflux during circulatory arrest in dogs at normothermia, and added to the effect of hypothermia.[77] They proposed that by membrane stabilisation, lignocaine might provide clinically useful brain protection during ischaemia by "saving the energy needed for maintaining the membrane potentials by ion pumping".

In another in vivo study using rats, Prenen et al. found that intrastriatal tetrodotoxin (another sodium channel blocker) significantly delayed deflection of the interstitial cortical potential which indicates significant cation shifts early in cerebral circulatory arrest.[78] Moreover, in rats allowed to survive for 24 hours following a standardised cerebral ischaemic insult, tetrodotoxin injected locally into the striatum almost completely prevented the ionic derangements characteristic of significant damage which were seen in other cerebral regions, and in the striatal areas of untreated controls. They suggested that ischaemic sodium influx into neurones may be a pivotal event in neuronal death. Further, they argued that blocking sodium channels and thereby preventing or slowing these changes may enhance neuronal recovery in a reversible injury.

A membrane stabilisation role for lignocaine in functional protection is supported by Fink who found that the C fibre action potential decrement in rabbit vagi incubated in a glucose free medium, was paradoxically delayed by addition of lignocaine to the incubation fluid.[79] Fink's observation by microelectrode studies that lignocaine reduced axonal potassium efflux after membrane pumps were disabled by hypoglycaemia, suggests that preservation of excitability was achieved by membrane stabilisation.

Although Gelb et al. noted that the sodium channel blockers flecainide and mexiletine, administered in high doses, were not effective in reducing infarct size in a feline model of focal ischaemia,[80] the model was particularly severe. The authors' conclusion, that the failure of these agents suggests that lignocaine does not provide protection by ion channel blockade, is unreasonable.

In addition to ion channel blockade, other aspects of membrane stabilisation may be relevant to lignocaine's neuroprotective properties. Lignocaine may participate in hydrophobic and electrostatic interactions with membrane phospholipids[81,82] and these effects may promote physical membrane stability.[83] Certainly, lignocaine reduces erythrocyte fragility[84] and reduces cell to cell fusion.[85] It has also been suggested that membrane stabilisation may reduce the release of free fatty acids and consequent generation of prostaglandins and toxic free radicals.[64] Finally, membrane stabilisation by lignocaine may prevent damaging mobilisation of intracellular calcium stores during ischaemia.[86]

TABLE 1

INVESTIGATIONS OF CEREBRAL FUNCTION PROTECTION BY LIGNOCAINE IN ISCHAEMIC INJURY

Authors	Model	Dose timing	Dose size	Dose regimen	Lesion	Outcome parameters
STUDIES DEMONSTRATING BENEFIT FROM LIGNOCAINE						
Evans et al.[54,55]	Cat	Pre-injury	Conventional	B	CAGE	SER
Evans et al.[57]	Cat	Post-injury	Conventional	B+I	CAGE	SER
Dutka et al.[58,59]	Dog	Post-injury	Conventional	B+I	CAGE	SER
Gelb et al.[62,63]	Cat	Pre-injury	Conventional	B	Focal ischaemia	SER
Shokunbi et al.[65]	Cat	Pre-injury	Conventional	B+I	Focal ischaemia	SER + histopathology
Sutherland et al.[64]	Rat	Pre-injury	Conventional	B	Incomplete global ischaemia	Histopathology
Rasool et al.[66]	Rabbit	Pre-injury	Conventional	B+I	Incomplete global ischaemia	SER
Nagao et al.[67]	Cat	Pre-injury	Conventional	B+I	Cerebral air exposure	SER
STUDIES DEMONSTRATING NO BENEFIT FROM LIGNOCAINE						
Shokunbi et al.[68]	Cat	Pre-injury	Higher than conventional	B+I	Focal ischaemia	Histopathology
Warner et al.[69]	Rat	Pre-injury	Higher than conventional	B	Incomplete global ischaemia	Histopathology

B = bolus dose only. B+I = bolus and continuous infusion.

Although it is difficult to relate the relevance of in vivo tetrodotoxin,[78] or extremely high doses of lignocaine,[77] to clinical lignocaine administration, sodium channel blockade and physical membrane stabilisation are established as potential neuroprotective mechanisms for lignocaine.

THE CEREBRAL METABOLIC RATE ($CMR0_2$) REDUCTION HYPOTHESIS

Early in vitro studies demonstrated that lignocaine in high concentrations reduced the oxygen consumption of rat brain cortex[87] and porcine brain mitochondria.[88] In an important in vivo experiment, Sakabe et al.[89] administered bolus doses of 3 and 15 mg/kg lignocaine to anaesthetised dogs and recorded reductions of $CMR0_2$ to 90% and 73% of baseline respectively. Maximal reduction of $CMR0_2$ coincided with peak lignocaine levels in sagittal sinus blood at 12 and 88 µmol/l for the 3 and 15 mg/kg doses respectively. In a further experiment, the $CMR0_2$ was increased significantly above baseline during seizures induced by a 27 mg/kg dose of lignocaine. Other authors have reported selective activation of hippocampal neurones by large "pre-epileptogenic" lignocaine doses.[90] It follows that the dose response profile of lignocaine in this regard is complex, and that high doses may result in disadvantageous energy consuming seizures.

Astrup et al. investigated the neuroelectric basis for reduction of cerebral metabolic rate by lignocaine.[91] They proposed that, in the healthy brain, the previously demonstrated membrane stabilising property of lignocaine[77] reduced the work of ion pumping and therefore $CMR0_2$. Lignocaine administered to dogs in a dose (160 mg/kg) sufficient to render the EEG isoelectric significantly reduced both the $CMR0_2$ and the cerebral metabolic rate for glucose (CMR_{gluc}). This was attributed to abolition of the metabolic cost of electrical activity, and was proposed to be similar to the effect of barbiturates. Lignocaine also produced a further reduction in $CMR0_2$ and CMR_{gluc} after the EEG had already been flattened with high dose thiopentone. The same was not observed for barbiturate when the drugs were administered in reverse order. Astrup et al. attributed this effect to ion channel blockade, reduced baseline ion leakage, and consequently reduced baseline ion pumping activity. Further investigation of lignocaine as an adjuvant to hypothermia in protection of the ischaemic brain was advocated.

TABLE 2

REPORTED HAEMODYNAMIC EFFECTS OF LIGNOCAINE

Authors	MAP healthy brain	MAP after injury*	ICP healthy brain	ICP after injury*	CBF healthy brain	CBF after injury*
CONVENTIONAL ANTIARRHYTHMIC DOSES OF LIGNOCAINE						
Donegan et al.[92]	Unchanged		Decrease			
Dutka et al.[59]						Increase
Evans et al.[52]		Decrease				
Evans et al.[55]		Decrease		Decrease		
Evans et al.[53]		Decrease		Decrease		
Evans et al.[57]		Decrease				
Johns et al.[93]	Unchanged					
Klein et al.[94]	Increase					
Lescanic et al.[95]					Unchanged	
McDermott et al.[70]		Decrease				
Nagao et al.[67]	Unchanged					Increase
Rasool et al.[66]	Unchanged	Unchanged	Unchanged	Decrease	Unchanged	Increase
Sakabe et al.[89]	Unchanged				Unchanged	
Shokunbi et al.[65]					Unchanged	Increase
Sutherland et al.[64]	Decrease					
Wiklund et al.[96]	Increase					
UNCONVENTIONALLY HIGH DOSES OF LIGNOCAINE						
Astrup et al.[91]	Decrease				Decrease	
Evans et al.[54]		Decrease		Decrease		
Lescanic et al.[95]					Decrease	
Milde and Milde[97]					Unchanged	
Sakabe et al.[89]	Decrease					
Shokunbi et al.[68]	Decrease					
Tommasino et al.[90]					Decrease	

* = compared with control animals not receiving lignocaine

Although the high lignocaine doses used in Astrup's study are not clinically relevant[91] a similar action at lower doses is possible. This may explain the significant reduction in $CMR0_2$ achieved at standard antiarrhythmic plasma lignocaine levels in Sakabe's trial.[89] Reduction of $CMR0_2$ by lignocaine may afford clinically useful cerebral protection in ischaemia.[91]

THE HAEMODYNAMIC BENEFIT HYPOTHESIS

Several authors suggest that haemodynamic alterations by lignocaine may contribute to protection of the ischaemic brain.[53,57,59,65-67]

The haemodynamic properties of lignocaine noted by various experimenters are listed in Table 2.[52,53,55,57,59,64-67,89-97]

Lignocaine in therapeutic doses appears to preserve CBF, reduce ICP, and prevent arterial hypertension after brain injury, while having no clear effect on these parameters in the healthy brain. How lignocaine achieves these haemodynamic alterations is unknown.[53] Reduction in mean arterial pressure (MAP) after brain injury may be due to a decrease in plasma catecholamines.[52] This effect may also explain the observation of an intracranial hypotensive effect for lignocaine during endotracheal suctioning,[92] endotracheal intubation (intravenous lignocaine),[98] and craniotomy.[99] Lignocaine has vasomotor effects but its dose/vasoactive response profile in the healthy circulation is complex. Conventional antiarrhythmic plasma concentrations cause vasoconstriction,[93,100] and unconventionally high concentrations cause vasoconstriction,[93,95] and vaso-dilation,[93,101,102] depending on the lignocaine dose and vascular bed studied.

A vasoconstrictive effect by lignocaine may contribute to reduction of ICP after brain injury by doses of lignocaine. However, the concomitant preservation of post-injury CBF despite attenuation of a rise in MAP suggests that cerebral vasoconstriction is not occurring. Alternatively, post-ischaemic preservation of CBF may be explained by a protective effect on cerebral blood vessels,[53] either by membrane stabilisation of endothelial cells or leucocyte deactivation (see later). Data is lacking on post-ischaemic effects of unconventionally high lignocaine doses/plasma levels on CBF, however it is notable that, in uninjured animals, such doses seem to reduce CBF and cause hypotension (Table 2). It follows that high lignocaine doses seem likely to haemodynamically disadvantage the brain.

It is concluded that, while the bases for the various haemodynamic effects of lignocaine are uncertain, these effects may contribute to its cerebroprotective properties. For example, depression of neural function after air embolism has been correlated against reduction of CBF[30] and lignocaine preserves CBF after this injury.[59] It is unlikely however, that haemodynamic alteration, whatever its basis, is the only cerebro-protective mechanism provided by lignocaine. In several studies,[66,67] a neuroelectrical protective effect was demonstrated before any haemodynamic benefit became significant, which suggested another concurrent protective process.

THE LEUCOCYTE DEACTIVATION HYPOTHESIS

The suggestion that leucocytes have an important role in DCI brain injury has been mentioned and is supported by data demonstrating that chemically induced leucocyte depletion preserves cerebral blood flow and function after air embolism in rabbits[32] and dogs.[23] Activated leucocytes have been observed to block microvessels in animal models of DCI[32] and other ischaemic injuries.[103,104] Of critical importance is the observation that leucocytes are activated and cause further damage, after restoration of perfusion to ischaemic tissue, for example following redistribution or resolution of a bubble in DCI, the so called "reperfusion injury".[105] The possibility of injury maturation by leucocyte activity after bubbles have been successfully resolved by HBO therapy is of considerable concern in DCI therapeutics, and it is fortunate that HBO also seems to have a role in reducing leucocyte activity.[36] It is also interesting that lignocaine seems to reduce a variety of leucocyte activities.[85,106-110]

Lignocaine in concentrations higher than conventional antiarrhythmic plasma levels decreases superoxide release,[108,110] oxygen consumption,[108] lysosomal enzyme release,[107] chemiluminescence[110] and bacterial killing[110] by stimulated leucocytes in vitro, and reduces leucocyte adhesion to venular epithelium in vivo.[106] Of particular interest are the findings of Luostarinen et al. who exposed the microvasculature of an everted hamster cheek pouch to standard laser induced injury and observed the rheological effects of topical saline, lignocaine, and other local anaesthetics.[85] When applied at the time of the injury, lignocaine prevented the irreversible thrombus formation which occurred in all control animals. In particular, injury site leucocyte-endothelium binding was markedly reduced in the lignocaine exposure trials. When applied 15 minutes after injury involving invariable thrombus formation, lignocaine produced restoration of flow in five of six trials. Moreover, during restoration of flow, leucocytes were observed to disadhere from endothelium and each other. The local anaesthetics tocainide and bupivacaine, trialled in the same series of experiments, had no antithrombotic effect.

All of these investigations involved exposure to concentrations of lignocaine higher than conventional safe antiarrhythmic levels. Although the actual leucocyte exposure concentration after diffusion in the Luostarinen experiment is unknown,[85] there is clearly doubt regarding the relevance of these results to DCI therapeutics since such plasma concentrations could not be safely achieved in humans. However, in a complex series of in vitro, in vivo, and human experiments using lignocaine in conventional antiarrhythmic concentrations, McGregor et al. recorded reduced leucocyte adherence, reduced inflammation and reduced migration of leucocytes into inflammatory exudate.[109] In the latter role, lignocaine was found to be more effective than methylprednisolone, a result described as "surprising". These authors proposed a possible protective role for lignocaine in myocardial infarction, arthritis, and "other autoimmune reactions". In another clinically relevant experiment, Peck et al.[110] recorded reduced superoxide anion release from human leucocytes exposed in vivo for at least 12 hours to plasma concentrations of lignocaine between 4-20 μmol/l.

The mechanism by which lignocaine modulates leucocyte activity is not clear, but it may involve alteration of cytoskeletal function[109,111] or inhibition of stimulus-response coupling at the cell membrane.[107] The impairment of neutrophil migration to sites of inflammation[109] is intriguing and, given the importance in this process of the CD18 glycoprotein receptor complex on the leucocyte and the intercellular adhesion molecule (ICAM-1) expressed on vascular endothelium,[112] it would be interesting to investigate the effect of lignocaine on expression of these molecules.

Whatever the molecular basis of its effect on leucocytes, lignocaine may preserve CBF in the injured brain by reducing leucocyte adherence to damaged endothelium. Functional protection and reduction of ischaemic damage may follow preservation of CBF. Lignocaine may also provide protection by reduction of cytotoxic/inflammatory substance elaboration by leucocytes.

THE MULTIPLE MECHANISM HYPOTHESIS

It is possible that lignocaine mediates neuroprotection through a combination of the above mechanisms. Indeed, lignocaine would appear to be an "ideal" approach to the biphasic pattern of CAGE injury, protecting neurones by membrane stabilisation or $CMRO_2$ reduction during initial vessel occlusion, and then ameliorating the secondary inflammatory changes after bubbles redistribute.

Discussion

The key questions to be answered in appraisal of the experimental data presented above are:

a are the models relevant to DCI; and
b do the data suggest a protective role for lignocaine and, if so, what is the ideal administration regimen?

None of the in vivo studies presented above involved treatment of decompression injury per se, and no trials of lignocaine were reported in disease states where autochthonous (tissue) bubbles may be contributory. However, a CAGE model was employed in three studies,[55,57,59] and these studies would seem directly relevant to the predominantly vascular mechanism of injury in cerebral DCI.[1] Other data come from animal models of focal and global cerebral ischaemia. These models share with DCI the common mechanism of ischaemic injury to neurones, but the relevance to DCI is not clear since intracorporeal bubble formation is not involved.[62-70] It is concluded that the models in which the protective action of lignocaine has been investigated may be classified as either substantially analogous to DCI,[55,57,59] or at least partially relevant.[62-70]

The clinical relevance of the somatosensory evoked response as an outcome measure in brain injury is sometimes questioned. Dutka et al.[59] conclude that SER recovery is physiologically significant and suggestive of possible functional benefit. This issue is discussed in depth by other authors.[113,114]

The data suggest a neuroprotective role for lignocaine in several forms of ischaemic injury. However, protection is not afforded in all models, and factors which may influence the protective capacity of lignocaine deserve attention. These include: the nature and severity of the injury, the dose and pattern of lignocaine administration and the timing of lignocaine administration with respect to the injury.

The nature and severity of the injury appear to be important determinants of lignocaine's efficacy. Significantly, lignocaine protected neuronal function in all experiments where a CAGE model was employed. There were mixed results in trials involving local and global cerebral ischaemia (Table 1). The two experiments demonstrating no benefit involved a relatively severe model of ischaemia. It is possible that the pool of compromised rather than dead neurones was too small for any intervention to affect outcome. The relevance of the nature and severity of the model to the neuroprotective efficacy of lignocaine has been emphasised by several authors,[65,68,70] with the general conclusion being that lignocaine seems to be most effective in transient and/or incomplete ischaemia, such as seen in CAGE. This may reflect an interim protective capability, for example, by membrane stabilisation,[78] which may be overwhelmed if ischaemia is either too severe or prolonged. Further, in CAGE, the functionally important post-embolic accumulation of leucocytes in the damaged circulation may be ameliorated by lignocaine, and this may contribute to its particular success in this injury.[59]

Both studies demonstrating no neuroprotective properties for lignocaine utilised doses larger than conventional antiarrhythmic regimens, whereas all studies demonstrating protection utilised conventional antiarrhythmic doses (Table 1). This observation may be coincidental. However, the finding that high doses of lignocaine selectively activate hippocampal neurones, increase metabolic stress, and thereby predispose to ischaemic injury,[70,115,116] may be important. Similarly, the consistent finding of CBF reduction with unconventionally high doses of lignocaine (Table 2) suggests that these doses may be haemodynamically disadvantageous as well as clinically impractical.

The pattern of lignocaine administration (ie. bolus only vs bolus plus infusion), may be an important determinant of efficacy. Several trials of lignocaine in ischaemic brain injuries have been performed where animals have been allowed to survive, injuries allowed to develop over seven days, and where outcome has been determined by histological examination of the brain.[64,69] One study found a marginal protection,[64] and the other found no protective effect[69] In both of these studies the animals were given a bolus dose of lignocaine only, indicating that the experimenters assumed lignocaine would exert no effect on the injury maturation process. Given that maturation of the lesion would involve a reperfusion injury with ongoing inflammatory changes mediated largely by leucocytes,[105] and given that lignocaine reduces the inflammatory activities of leucocytes,[106-110] the failure to administer an ongoing lignocaine infusion in these models seems to be a methodological flaw. Even in shorter term experiments, a possible decrement in protective effect as plasma lignocaine levels fall after the bolus (such as demonstrated with $CMR0_2$ reduction[89]) would suggest that a bolus plus infusion regimen is the most appropriate for assessing protection.

Finally, although the effect of significantly delayed administration of lignocaine after ischaemic brain injury is not addressed by any of the studies, it must be assumed that the possible benefit will decline as delay increases. In all of the in vivo experiments described, lignocaine was administered either before or within the 10 minutes following injury. There is no indication of maximum administration delay before protective effect would decline or be absent altogether. It can be hypothesised that protection on the basis of membrane stabilisation and prevention of ischaemic ion fluxes would require either prophylactic or immediate post injury administration. Protection by modulation of injury maturation may be afforded by delayed administration, but no data exist to support or refute this theory.

On the basis of the experimental data reported it is hypothesised that lignocaine, given in a conventional antiarrhythmic bolus plus infusion regime, beginning as soon as possible after the onset of neurological DCI and continuing for a period of at least 48 hours, may provide additional clinical benefit to standard HBO treatment.

Current investigations

A randomised, double blinded, controlled trial of lignocaine in prophylaxis of embolic brain injury in valve replacement cardiac surgery patients has been initiated at Greenlane Hospital, Auckland, New Zealand. This patient population has been chosen because of the significance of the problem in its own right, the pathophysiological similarities to CAGE in divers and the comparative methodological ease with which the population may be studied. Patients 20-70 years old undergoing valve replacement have preoperative neurological examination and comprehensive neuropsychological testing. At surgery a blinded infusion of lignocaine (in standard antiarrhythmic doses) or saline is initiated before cardiopulmonary bypass, and continues for 48 hours. A colour flow Doppler interfaced with an emboli signal counting microprocessor is used to quantify emboli activity in the right carotid artery during surgery. The neuropsychological examination is repeated at 8 days, 8 weeks, and 6 months after surgery. Postoperative decrement and recovery in the two groups will be compared. Twenty three patients had completed the in-patient portion of the protocol, since its inception in December 1994, by May 1995.

A protocol has been generated for a randomised, double blinded, controlled trial of lignocaine as an adjunct to HBO in the treatment of DCI. This awaits completion of the heliox trial at the Royal New Zealand Navy Hyperbaric Unit and other Australasian Hyperbaric Units.

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This paper was accepted as the required thesis for the award of the Diploma of Diving and Hyperbaric Medicine to Dr Mitchell.

Dr S.J Mitchell BHB MB ChB is a Full time Medical Officer at the Slark Hyperbaric Unit, Royal New Zealand Navy Hospital, Devonport, Auckland, New Zealand. Phone (64) (09) 445 5922. Fax (64) (09) 445 5941.

PROVISIONAL REPORT ON AUSTRALIAN DIVING-RELATED DEATHS IN 1992

Douglas Walker

Introduction

Of the 18 deaths in 1992 four were breath-hold (snorkel) divers, nine used scuba, four had a hose supply (one was using a cylinder air supply while the others were compressor (hookah) supplied) and a single diver was using a rebreather set.

Medical conditions were recorded for three of the breath-hold, five of the scuba divers and two of those using hookah. However in several instances the findings were either incidental or possibly so. In only one was a possible missed medical diagnosis apparent and it cannot be known whether the patient gave a full history to her doctor (case SC 92/8). The asthma factor has uncertain significance in case H 92/2 as there were significant other factors (fatigue, cold, rough water, inexperience) present.

Trauma to the head was a factor in two cases, a breath-hold diver and a military diver, and general trauma dramatically ended the life of a hose supplied diver in a dam.

Breath-hold diving deaths

BH 92/1

Because the sea was too calm for them to go surfing or fishing the two friends decided they would go diving. Although the victim was to be snorkelling, something he did infrequently, he was not a spear fisherman. The victim's friend (buddy) was to be using scuba. He was trained but had made no dives in the previous 12 months. They entered the water from rocks and swam out a short distance before the buddy descended leaving the victim at the surface. He was very surprised when, about 5 minutes later, he saw his friend lying on the sea bed. as he did not consider him capable of swimming to that depth (5 m). The victim was without his mask, snorkel and fins and it was apparent that he was unconscious. The buddy described trying, unsuccessfully, to give him air from his regulator and then pulling him up to the surface after partly inflating his buoyancy vest.