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A RANDOMISED PROSPECTIVE TRIAL OF LIGNOCAINE IN THE MANAGEMENT OF ACUTE NEUROLOGICAL DECOMPRESSION ILLNESS – AN UPDATE

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Key Words

Drugs, decompression illness, treatment.

Abstract

There are good reasons to believe, from both animal experimental data and human studies, that lignocaine, given alone or in combination with hyperbaric oxygen, should improve the outcome of acute neurological decompression illness (DCI). The evidence supports the hypothesis that the cases in which there is brain involvement will benefit particularly. Unfortunately, it is only in a small minority of cases of DCI that there is overt evidence of brain involvement. Since DCI is, in any case, a rare disease, studying the potential benefit of lignocaine in a human population will require a multi-centre approach and a large number of centres will be needed if a result is to be reached in a reasonable time. The logistics of reaching an agreed protocol and coordinating the trial will be considerable. However, such constraints do not render clinical studies of this kind either impossible or impractical. My colleagues and I believe that it is possible to conduct a randomised, double-blinded trial of lignocaine in acute neurological DCI.

What will be more difficult will be to find a willing funding agency. The original proposal for this study was to be funded by the US Navy. Unknown to us at the outset, it is a requirement of US law that all studies funded by the US Department of Defense that involve human volunteers must provide for informed consent before the volunteer's entry into the trial. Since the study population is required to show evidence of brain disease, which renders the individual incapable of giving informed consent, this condition cannot be met. As divers do not always dive with their next of kin or legal representative, and because the treatment of DCI should not be delayed so that such a person can be contacted and asked to consent, it is impractical to attempt this study using US Navy funding. With any luck, an alternative source of funding will be found. In the meantime, the study is on hold.

Introduction

A workshop sponsored by the United States Special Operations Command (USSOCOM) and conducted by the Undersea and Hyperbaric Medical Society (UHMS) at its meeting in Anchorage, Alaska on 30 April 1996 examined the management of diving casualties in the tactical Special Operations environment.[1] Several issues with respect to the treatment of decompression illness in these operations emerged during the workshop. Among these was the issue of adjuncts to recompression therapy.

Most commercial and military diving operations are conducted so that any victim of DCI can be recompressed rapidly. When treated without delay, the success rate for treating these casualties has been reported by several authors to be over 95% for a single treatment.[2-4] However, Special Operations are often conducted in remote areas where there may be considerable delay in access to recompression facilities, with an accordingly higher probability of severe or refractory disease as a result.

It would be of great benefit to have a medication which would relieve some of the negative impact of delays inherent in remote military operations. Equally, in civilian life, a treatment that could slow the progression of disease during transit to a compression chamber would be of value, particularly when the transit time is great. Lignocaine is a widely used drug with the potential to have this effect. However there is, as yet, no evidence from human clinical studies of its efficacy in DCI. This is part of a larger problem in the management of DCI. Despite more than 150 years of observation and study, the diagnosis of DCI is based entirely on the patient's history and examination, and treatment is limited to the provision of adequate hydration and largely empirical hyperbaric oxygen protocols.[5,6] To date, no randomised, blinded, prospective trial of any therapeutic intervention for DCI has been reported in the literature.

There are many reasons why this is the case. DCI is a rare condition. World-wide there are probably no more than 5,000 cases a year. Treatment is commonly provided by hyperbaric units that receive fewer than 100 a year. Of those cases, only a small minority have serious neurological manifestations. Consequently, for any prospective clinical trial of the management of serious neurological DCI to be completed in a reasonable time, more than one hyperbaric unit needs to be involved. With units being separated by distance and, not infrequently, language it is hardly surprising that the logistic difficulties of organising a multi-centre trial have proved to be considerable.

In 1998, USSOCOM agreed to fund a proposal to determine if it is feasible to conduct a randomised, prospective, double-blinded trial of lignocaine in the management of acute neurological DCI. I undertook this study with Dr Ed Thalmann of Duke University and this report is a summary of our deliberations and conclusions.

The potential benefit of lignocaine

There is good evidence that the class 1b anti-arrhythmic agent and local anaesthetic lignocaine may ameliorate the effects of bubble embolism to the brain. Evans et al. using a feline animal model were the first to show that lignocaine given prophylactically in clinically relevant doses preserves neuro-electrical function after arterial gas embolism (AGE).[7] Subsequent in vivo studies, employing a variety of gas embolism protocols, have demonstrated that lignocaine preserves neuro-electrical function and blood flow;[8-10] reduces the extent of cerebral oedema and lowers intracranial pressure.[11-13] There have been similar findings in models of focal and global cerebral ischaemia.[14-17]

Possible mechanisms whereby lignocaine causes these observed effects include inhibiting the transmembrane ion shifts that occur early in neuronal ischaemia;[18-22] reducing the cerebral metabolic rate;[23,24] modulation of leucocyte activity and reducing the release of ischaemic excitotoxins.[25-34]

Because of the considerable body of evidence for believing that lignocaine may be beneficial in the management of DCI, it has been used at a number of centres although in a somewhat haphazard manner. The results of two such interventions have been published as case studies and, although anecdotal, these provide some evidence that lignocaine at least has no detrimental effects.[35,36] Showing efficacy, however, will require a formal study. Of the many potential candidate drugs for consideration in the management of acute neurological DCI we feel that lignocaine offers the best chance of success at the present time.

Study population

In the First World, the standard of care for the management of acute DCI is rehydration, recompression and the provision of oxygen. There are a considerable variety of protocols for the delivery of these agents.[6] Since it would be impossible from an ethical perspective to deny First World victims of DCI a conventional recompression protocol, any investigation of the efficacy of lignocaine on this population must be as an adjunct to recompression and oxygen. Clearly, for this approach to be successful, every effort will have to be made to ensure that the hyperbaric limb of the trial is as consistent as possible between participating units.

An alternative approach would be to investigate the efficacy of lignocaine in a population of divers who do not normally have access to recompression facilities. Such an approach would evaluate the drug in a situation that closely resembles the likely scenario to which USSOCOM forces may be exposed. There are substantial populations of diving fishermen on the Mosquito coast of Central America and in the Far East who do not routinely have access to recompression facilities. However, the political, logistic and ethical difficulties in conducting such a study render this option impractical at present.

Participating centres

A major part of the feasibility study was to identify centres that would be willing to take part in the study. The criteria that such centres should satisfy are:

1 Willing to comply with a standard therapeutic protocol (see below).
2 Appropriate ethical supervision of clinical protocols.
3 Willing to complete and submit the documentation in a timely fashion.
4 Availability and cost of monitored beds (if necessary).
5 Willing to follow up patients.

We decided at the outset that, in order to make communication as easy as possible, only English-speaking countries would be considered. We approached a number of centres in the USA, UK and the Antipodes and Table 1 shows the caseload of those centres that fulfilled the above criteria. As will be discussed later, another important consideration is that the more centres that are involved, the more difficult the coordination of the trial is likely to be. Ideally a small number of centres, each with a large caseload, would be involved.

TABLE 1

ANNUAL ACUTE NEUROLOGICAL DCI CASES WITH EVIDENCE OF CEREBRAL INVOLVEMENT AT POTENTIAL PARTICIPATING CENTRES

Unit	Yearly cases	Suitable for trial
Townsville	90-110	20-30
Melbourne	~80	~20
West Palm Beach	75-90	10-20
INM, Alverstoke	50-70	10-15
Plymouth	35-50	10-15
Poole	50-60	10-12
Aberdeen	15-30	5-9
Miami	50-70	5-7
Sydney	50-60	5-6
Honolulu	60-80	4-5
Fremantle	~30	4-5
Adelaide	20-25	4-5
Christchurch	30-40	3-5
Taverner	20-40	2-4
Auckland	50-60	2-3
Brisbane	~20	2
TOTALS	**725-915**	**106-163**

Criteria for entry into the trial

It is important that only cases of DCI are entered into the trial. Consequently no patient with a latent interval of more than 24 hours from completion of the last dive and the onset of manifestations of DCI should be admitted because the diagnosis is likely to have an element of doubt associated with it. Equally, there is no point in admitting cases in which there has been an apparently complete recovery, since it would be impossible to score any therapeutic benefit. This could be taken one step further, with a minimum score being set as an entry criterion.

Another potentially confounding factor is the delay to treatment. This varies enormously between centres, with those in the UK generally having the shortest delays and those in the Antipodes the longest. We did not consider that it would be appropriate to exclude cases based on delay to treatment. Not only is there no recognised cut-off at which treatment has been shown to be ineffective, such a policy could potentially exclude a large proportion of cases. Instead, it may be necessary to stratify cases, based on delay to treatment, when the time comes to analyse the data.

The justification for using lignocaine in DCI is based on its effects on the brain. It is therefore considered necessary that there should be at least one manifestation that is referable to involvement of the brain, such as a history of loss of consciousness; sensory or motor loss compatible with a cortical lesion, perturbation of any special sense and any positive finding on the mini mental examination. Since involvement of the brain is relatively uncommon in DCI, this requirement will necessarily limit the number of cases that can be entered into the trial.

The contra-indications for the use of lignocaine will also exclude potential cases from inclusion. These include known sensitivity to the drug, known pregnancy or liver disease and patients taking calcium channel blockers. In addition, patients who have treated themselves with or who have received a non-steroidal anti-inflammatory drug (NSAID) or a steroid preparation (other than using an oral inhaler) should be excluded on the grounds that they have been used therapeutically in DCI and may confound the trial.

In those centres that require patients receiving lignocaine infusions to be in a monitored bed (in ICU, CCU or equivalent), if no such bed is available, no patients can be entered into the trial until a bed is free.

Potential clinical protocol

Although developing a detailed method was not an objective of our study, we did need to consider in outline how such a study might be undertaken. We were greatly helped in this regard by Dr Simon Mitchell who had developed a detailed protocol while working in Auckland. The main steps in the clinical protocol would be:

1 Patient arrives at treating facility and appropriate stabilisation measures are instituted.
2 History and physical examination are completed using standard forms.
3 Determination made as to whether the patient meets the entry criteria.
4 If entry criteria are met and informed consent obtained, the patient is entered into study.
5 IV infusion started and blood samples for specified clinical tests drawn.
6 Drug administration is begun just before recompression at rate specified in the protocol. Subject and all treating personnel are blinded as to whether they are administering lignocaine or placebo.
7 Recompression protocol started.
8 Blood for lignocaine level drawn 8 hours after IV infusion was begun.
9 Recompression protocol completed, lignocaine infusion is continued for 24 hours from the start of infusion, then stopped.
10 Patient is reassessed 12-24 hours after initial treatment. Follow on treatments conducted as appropriate. Lignocaine is not administered during follow up treatments.
11 Patient's condition at discharge is recorded.
12 Patient follow up interviews to be conducted at one week, one month and one year after discharge.

Severity and outcome measures

In preparing his protocol, Dr Mitchell recognised that a formal system was required to score the severity of disease and the extent of recovery from DCI (i.e. treatment outcome). This is particularly important since there is no quantitative or even qualitative clinical test for the condition. The score that results from the application of such a system must be demonstrated to correlate with clinical or other indices of severity. In addition, for such a system to be useful in a multi-centre trial, it must be shown to be applied consistently between observers. Mitchell et al. published such a scoring system in 1998.[37] Although the scoring system is mathematically quite complex, it lends itself to being processed on a spreadsheet program. In terms of the information required from the examining physician it is remarkably simple. Each manifestation is allotted a value of 0-3: 0 = nil; 1 mild; 2 moderate; 3 severe. Another advantage of the system is that it is comprehensive in that it addresses all the potential manifestations of DCI, rather than focusing purely on those involving the nervous system. Finally, the system takes account of important characteristics of each manifestation: how specific it is to DCI; its natural history; its potential to incapacitate the victim and whether other manifestations are co-dependent on it. In this respect, it is considered to be the best system yet developed and appropriate for use in this study.

Since it was published the scoring system has been validated by Holley, who retrospectively scored 100 consecutive admissions with DCI to the Auckland hyperbaric unit.[38] He used the number of hyperbaric treatments the patient received as an index of severity and correlated this against the severity score on admission. He found a linear correlation coefficient, r, of 0.8. Using a score of 25 as a cut-off, he found that 77% of those with a score above 25 (more severely affected) were left with residua or developed sequelae; 89% of those scoring 25 or less had no residua or sequelae. It appears that the scoring system does represent a valid means of quantifying the severity of disease.

There has been no attempt so far to assess the fidelity of the scoring system between observers. While it would be possible to undertake such an assessment using case studies, it would be a less convincing test than using the scoring system live with two observers scoring the same patient independently. The reason being that in a multi-centre trial the scoring system would have to be used live, case study information having already been filtered by the examining physician. We feel that such a trial would have to be undertaken before the scoring system is used in a clinical trial of lignocaine.

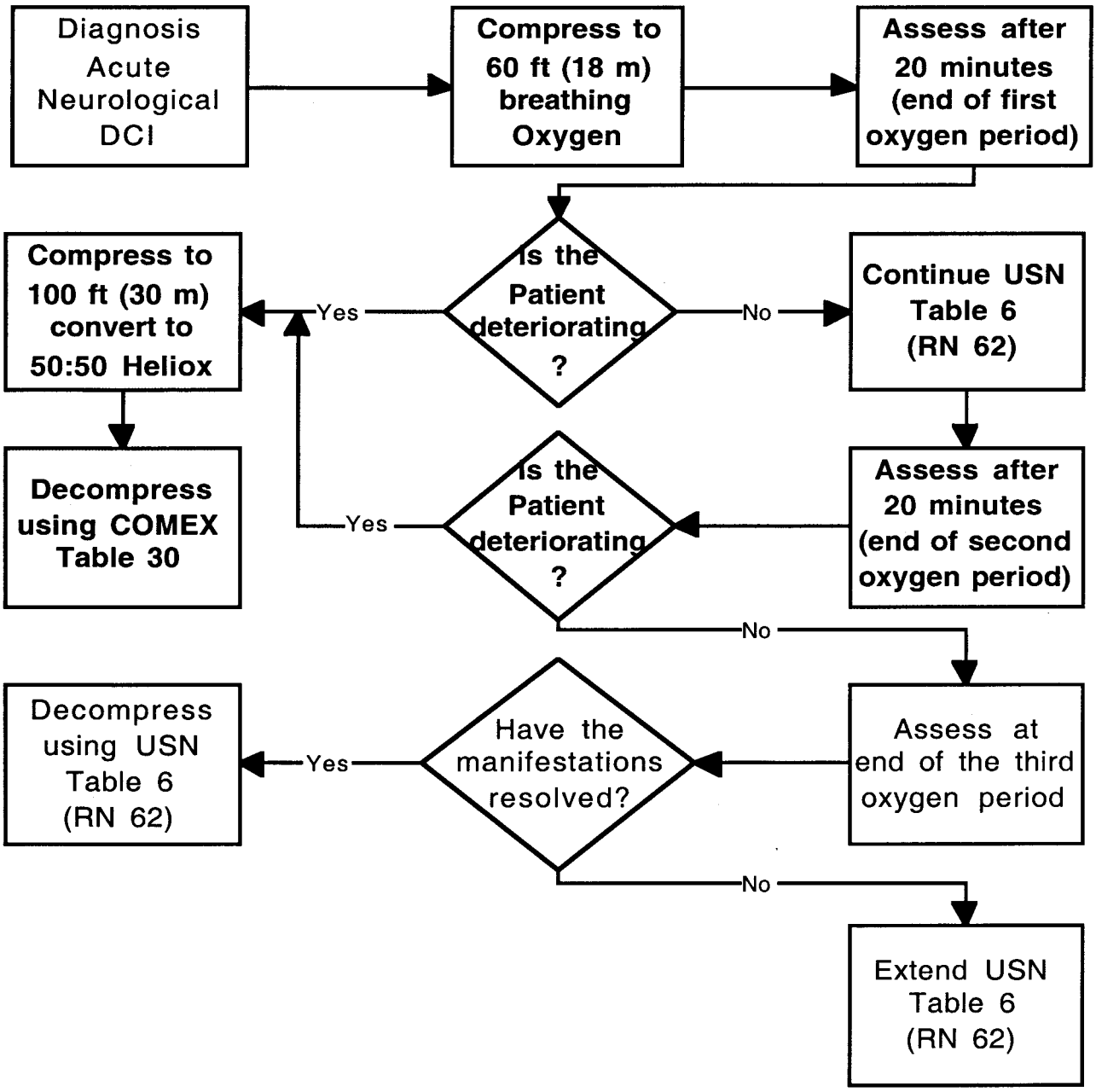

Figure 1. Outline recompression protocol for a multi-centre trial of lignocaine in the management of acute DCI

Subsequent patient evaluation

In the outline protocol it is proposed that patients should be re-evaluated one week, one month and one year after discharge. This is likely to be difficult to conduct in centres in which a large proportion of the caseload is tourists. Potential solutions to this problem are to consider follow up by telephone or for patients to be followed up by their family physician, who consults the original treating centre as necessary.

Proposed hyperbaric protocol

In discussions with the various units we visited it was apparent that one protocol, with small variations, is predominantly used. This is the US Navy Table 6 (RN Table 62), with extensions at 18 and 9 m as determined by the treating physician and based on the response of the patient.[6] Almost universally the patient is assessed at the completion of the first or second oxygen period at 18 m and, only if the patient is deteriorating or has very severe static neurological manifestations, is he or she transferred to a deeper table. Again, almost universally, the deeper table selected is the COMEX 30 table with the patient breathing a 50:50 heliox mixture while deeper than 18 m.[6] It is therefore likely that the hyperbaric protocol, subject to the agreement of the participating units, will be something along the lines of Figure 1.

For repeat treatments, there is a wide disparity in the protocols used. However, most centres expressed a willingness to be flexible. In many centres, if there are residual motor signs, the first re-treatment is a further US Navy Table 6 (RN 62). In the absence of motor signs, or for subsequent treatments, a short, shallow oxygen table is used almost universally and this may be a USN Table 5 (RN 61) or a 60-90 minute soak at various depths (2.0-2.8 bar) on oxygen with a slow (10-30 minute) bleed to the surface. In the interest of consistency it will be desirable to specify a re-treatment protocol and a table such as the Royal Navy Table 66 (Table 2) would be appropriate. When using this table, the attendant should breathe oxygen for the final 20 minute oxygen period and the ten minute ascent to the surface. There was consensus with the view that re-treatments should continue on a once- or twice-daily basis until there is no further sustained incremental improvement in the residual manifestation(s).

Number of cases and controls

In order to justify the study we must determine whether or not there will be sufficient patients to either accept or reject the null hypothesis at a certain level of confidence. The null hypothesis (H0), is that lignocaine has no effect on the outcome of acute neurological DCI. If we reject H0 we want to be 95% sure that the rejection was not due to chance alone, that is there is only a 5% chance that the H0 was rejected when it is actually true. This means we want the Type 1 error to be 5% or less. We must also be sure that we do not accept the null hypothesis when it is in fact false. This Type 2 error is usually set at 20% for most medical studies. If the Type 2 error is 20% the power of the study is 80%. The appropriate formula is:

$$Z_\alpha - Z_\beta = \frac{\bar{x}_1 - \bar{x}_2}{sd\sqrt{1/n_1 + 1/n_2}} \qquad (1)$$

where:
Z_α = Z score for 5% Type 1 error (1.96)
Z_β = Z score for 20% Type 2 error (-0.845)
$\bar{x}_1$ = mean score for control group
$\bar{x}_2$ = mean score for lignocaine group
n_1 = n_2 = number of subjects in each group
sd = standard deviation of scores

Equation 1 is easily solved for n, the number in each group:

$$n = \frac{2}{\left(\frac{(\bar{x}_1 - \bar{x}_2)}{sd\langle (Z_\varepsilon - Z_\beta)}\right)^2} \qquad (2)$$

TABLE 2
ROYAL NAVY TREATMENT TABLE 66

Gauge Depth in metres of seawater (feet)		Stops/Ascent in minutes (breathing mix)		Elapsed Time (hours and minutes)		Rate of Ascent msw/min (fsw/min)
14	**(45 fsw)**	**30**	**(O_2)**	**00:00 –**	**00:30**	
14	(45 fsw)	5	(Air)	00:30 –	00:35	
14	**(45 fsw)**	**30**	**(O_2)**	**00:35 –**	**01:05**	
14	(45 fsw)	5	(Air)	01:05 –	01:10	
14	**(45 fsw)**	**20**	**(O_2)**	**01:10 –**	**01:30**	
14-0	(45 fsw-0)	10	(O_2)	01:30 –	1:40	1.4m (4.5 fsw)
Surface					**01:40**	

Since the standard deviation is not known we use the relative mean difference $\frac{(\overline{x_1} - \overline{x_2})}{sd}$ to estimate the size of the effect. The convention is that if the relative mean difference is 0.1 or less there is no effect. If it is 0.3 there is a slight effect, 0.5 a moderate effect, and if it is 0.9 there is a large effect. Substituting these values for Z we obtain table 3.

TABLE 3

NUMBER OF SUBJECTS REQUIRED

Relative mean difference	Number of subjects in each group
0.1	1,574
0.3	175
0.5	63
0.9	18

Lignocaine levels

In Dr Mitchell's original protocol, he proposed that a plasma lignocaine level be taken at 8 and 24 hours into the infusion and the infusion rate adjusted accordingly. The reasons for this were:

a. To avoid toxicity and
b. To ensure that the blood level was in the therapeutic range.

For those receiving the placebo, a system of sham results should be in place whereby the reporting laboratory would report a value determined by the investigators.

In discussing this with the centres visited, it rapidly became apparent that the measurement of plasma lignocaine levels was not a routine procedure and many laboratories would be unable to process samples in a timely fashion unless an analytical kit were provided. In other instances the samples would have to be sent to a reference laboratory. Either option would be expensive and the latter would also be time consuming to the point that it may not be possible to use the resulting data while the infusion was in progress.

In assessing why measurement of the lignocaine level should be undertaken we concluded that a check is necessary to ensure that patients who were supposed to receive the drug did so and those who were not supposed to did not. It was the experience of a number of centres that the infusion rate proposed, a pump-controlled bolus of 0.5 mg/kg over 20 minutes followed by 120 ml of a 2 mg/ml solution (240 mg) over the next hour, 60 ml (120 mg) over the next hour and 45 ml (90 mg) per hour thereafter, invariably results in a therapeutic dose in the otherwise healthy young patients that are representative of the diving population. Equally, an infusion lasting only 24 hours is unlikely to result in lignocaine toxicity. It is therefore considered appropriate that a single level should be taken just before the infusion is discontinued and that these samples be frozen and batched for processing at a reference laboratory.

Ethical clearance

For this trial to work each centre must conform to a single protocol. Ethical approval for the protocol would have to be granted not only by the US Navy but the human use committees of each participating centre. We do not underestimate the difficulty involved in getting such approval. It will be considerable and will increase with each centre that is added to the protocol. Although the institutional ethics committees at the centres visited offer a processing time of between one and two months, it is inevitable that some rewording, additions or deletions of the first draft will be required to satisfy many of them. Potentially, some of these will be conflicting. The result is likely to be a protracted process of serial revisions, each requiring as long as the slowest review body takes to complete the process, until a final draft is agreed, assuming that this is possible. It is considered that a period of no less than six months should be allowed for this process and longer if more than six centres participate.

Informed consent

In the course of discussing an outline protocol with a number of centres it became apparent that the study contained a potential ethical issue. As the justification for studying the use of lignocaine in the management of DCI is based on its effects on the brain, it is almost certainly necessary to require evidence of involvement of the brain in the subjects. If there is evidence of brain dysfunction, can patients give informed consent to participate in the trial?

Having consulted the director of the US Navy Clinical Investigation Program, the answer to the question is "No." Furthermore, there is a section of the United States Code (No. 10 USC 980) which reads: "Funds appropriated to the Department of Defense (DoD) may not be used for research involving a human being as an experimental subject unless (1) the informed consent of the subject is obtained in advance; or (2) in the case of research intended to be beneficial to the subject, the informed consent of the subject or a legal representative of the subject is obtained in advance." This requirement is imperative, non-negotiable, and can not be waived. If gaining the patient's informed consent is not possible because the patient has brain disease, this would jeopardise the US DoD funding such a trial. Furthermore, 10 USC 980 precludes any DoD study from attempting to invoke legislation known as 21 CFR 50.23, which was written precisely to allow these types of

emergency studies, with minimal time to contact third party consent relatives, to proceed without specific informed consent of the subjects.

We briefly considered the possibility of gaining informed consent from divers prior to their undertaking the dive that causes DCI. It would require a herculean effort to approach, let alone gain the consent of just the estimated 5 million divers in the USA. It would be equally difficult to recruit those who hail from Canada, the UK or the Antipodes. The problem is that there are numerous umbrella organisations for divers and many divers belong to no organisation whatsoever. This idea was therefore quickly rejected. It would be equally difficult to try to gather the consent of a partner, parent, legal guardian or legal counsel who could provide consent on the patient's behalf. Except for married divers who choose to dive with their spouse (a very small minority of the sports diving population) it is most unlikely that anybody who could consent on the patient's behalf will arrive at the hyperbaric unit with the casualty. Since acute neurological DCI represents a medical emergency, delaying treatment while attempting to contact such a person by telephone would be unethical. The provisions of 10 USC 980 have halted this study in its tracks and precludes it being funded by the US DoD. However, in all other important respects, we feel that the study is perfectly feasible although it will be difficult and expensive to undertake.

Conclusions

At the outset of this study we predicted that the most difficult part of this study would be to find suitable participating centres. This turned out not to be the case. There is clearly much enthusiasm for conducting randomised, double-blinded trials in DCI. There are, however, substantial hurdles that will have to be overcome to see such a project through to fruition. Many of these arise because of the need to involve a large number of centres if results are to be available in a reasonable time frame. The logistics of reaching an agreed protocol and coordinating the trial will be considerable, particularly if the entry criteria to the study are restrictive, as they are in this case. However, these constraints do not render clinical studies of this kind either impossible or impractical. We believe that it is possible to conduct a randomised, double-blinded trial of lignocaine in acute neurological DCI.

A difficulty, which I have not covered, is that this trial will be very expensive to conduct and, given the limited number of organisations with deep pockets that are likely to fund such research, this will limit the rate of progress in the future. An important funding organisation in diving medicine is the US Navy. The limitation to getting this study funded by the US Navy turned out to be the constraints placed by the US Congress on how the DoD conducts its clinical research. This constraint is unlikely to be removed in the near term, if ever. Thus, if clinical studies of this kind are to be funded by the US Navy, there must be no difficulty with obtaining proper informed consent. Alternatively, a more liberal source of funding will have to be found.

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AUDIENCE PARTICIPATION

Chris Acott, Adelaide

I have two case histories. The Diver Emergency Service, based at the Royal Adelaide Hospital (RAH) occasionally gets calls from chambers in Thailand where there are a lot of fishermen divers. Three weeks ago I was rung as they had a diver who was paraplegic, with no bladder or anal control. He had presented after a long delay. As they had treated him twice with a US Navy table 6 without improvement they rang me for advice. I suggested that they started him on a lignocaine infusion. He made a full recovery and walked out of hospital. The other was in the RAH. He had six Table 6 treatments and was still hemiparetic. He was starting on a lignocaine infusion just before I left. It will be very interesting to see how he went when I get home.

James Francis

I have also seen this sort of Lazarus effect with lignocaine. I think the potential is wonderful but to get it as an indicated use of the drug we will have to have some trials to prove that it works and, at the moment, I have got no idea how we are going to get this expensive trial funded. We calculated the cost of the trial, for the benefit of the US Navy, to be around $600,000 to $1,000,000 to do.

Mike Bennett, Sydney

In view of the of stories that Chris has mentioned, is it ethical to deliberately not give half of them lignocaine? How long is that trial going to be ethical for us to do, let alone US Navy regulations.

James Francis

I suppose if there is a steady drip of case reports in the literature of this Lazarus type effect, eventually that will provide sufficient weight of evidence for its use in DCI becoming an indicated entity. It really depends upon whether people like Chris and I write up the cases. I have not written up either of the two that I have used lignocaine with. Are you going to write yours up Chris? Lignocaine is used sporadically all over the place now. One of the things I have had to tell people is even if they want to use lignocaine they should wait and hold back and not use it until the trail is completed. Some people use it almost routinely now and as soon as that becomes the case, of course one cannot do the trial.

John Knight, Melbourne

If you are getting Lazarus type results, you are back in the situation of the early antibiotics. Nobody ever did a controlled trial of streptomycin in tuberculosis or penicillin in infected wounds. The results were so different from what had been happening before that it would have been unethical not to treat the patients.

James Francis

That is true but out of date. In the UK we have the National Institute of Clinical Excellence or NICE for short. These people review medications for use in the National Health Service (NHS). Their decisions are evidence based. On the recommendations of this NICE committee people are allowed or not allowed to use drugs in the NHS. There was no NICE committee when antibiotics were being developed. Just as well, but unfortunately we live in a world where one cannot work like that.

David Taylor, Melbourne

While I was at Duke we had a couple of severe spinal hits where they were commenced on lignocaine within half an hour. In one case there was no effect at all. He got worse and we ended up saturating him.

James Francis

This is the point about doing trials. One may get wonderful results reported with a particular drug or regime, but very rarely are the failures reported. If one has done a proper controlled trial that should come out in the wash up.

Mike Davis, Christchurch

I'd like David just to put the other side of the coin. We have used lignocaine in about 10 divers over the last few years in Christchurch. So far I have not seen any enhanced benefit from its use in anyone. So I don't think there is any problem about the ethics of a trial of this nature.

Mike Bennett, Sydney

Our experience at the Prince of Wales Hospital is that one or two have some benefit. But for most there is no apparent change to their course. However in most cases, we are giving lignocaine later than the trial was contemplating.

Barbara Trytko, Prince of Wales Hospital

I have used it in two patients who had cerebral symptoms and were started on it before being retrieved. Both patients did very well.

James Francis

The problem is that cerebral DCI is notoriously good at getting better. The spinal ones often have major residua. Another reason to need a large number of cases to show a difference.

Drew Richardson, PADI

Is it possible to do a pilot study, scale it down a little bit to make it cheaper?

James Francis

The problem is if one did that the trial would not have the power to answer the question. It is not really worth doing a study unless there are enough cases to answer the question. But each case costs money. The patients will stay longer than they normally do. Additional staff will be needed. Monitoring in full is expensive. A study like this is only worth while if it gives clear answers.

Mike Bennett

Unfortunately the words "pilot study" is often code for " I do not have the time, money or inclination to do the proper job".

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