risks associated with short courses of Tenoxicam are well known and unlikely to prove a problem during the remainder of this trial. There have been no attributable side-effects to March 1997.

Based on an expected rate of complete resolution of 75% in the placebo group and an assessment that an improvement to 88% would be clinically significant in the active drug group, it is anticipated that about 180 patients will be needed to have a 90% chance of detecting such a difference with 95% confidence. In order to complete such a study within a reasonable time, other centres have been invited to contribute their patients. In March 1997 the Prince of Wales Hospital and HMAS PENGUIN were actively involved. Two other established Australian centres are to join shortly.

Progress

By March 1997 we had enrolled 26 individuals in the trial. There have been five other cases who did not enter the trial. Three chose to decline the opportunity while one was not asked and in one there was a contraindication to NSAID administration. The randomisation codes have not been broken for this report.

The majority (18 cases) fell into grade two on the admission scale, while the other four groups have contributed 2 cases each. The average number of treatments before discharge is 2.6 at this early stage.

Three cases have not yet had their 6 week follow-up. At this appointment 18 cases had complete resolution of symptoms while some symptoms persisted in 5. This represents a rate of less than complete resolution (discharge level >1) of 21.7%. Lying between the previously published rate for this unit (27%) and the proposed rate for a demonstration of clinically significant efficacy (12%), this result looks promising.

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LIGNOCAINE AND NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AS ADJUVANT THERAPY IN TREATING DECOMPRESSION ILLNESS.

David Cosh

Key Words
Decompression illness, drugs, treatment.

Lignocaine

Simon Mitchell has reviewed the evidence supporting the use of lignocaine, an aminoethylamide local anaesthetic with class 1B anti-arrhythmic properties, as adjuvant therapy to the accepted modalities of compression and hyperbaric oxygen (HBO) in the treatment of decompression illness (DCI).[1] It is well known that tissue damage secondary to the presence of intravascular and extravascular bubbles can be caused by ischaemia, mechanical effects and inflammation. Nellgård et al. have demonstrated a potent anti-inflammatory effect of lignocaine in a rat model of bowel obstruction where jejunal fluid loss was converted into net fluid absorption by the administration of intravenous lignocaine in conventional doses (2 mg/kg). Lignocaine applied topically to the serosa proximal to the ligation was also effective.[2,3]

It is unlikely that the anti-inflammatory effect of lignocaine is solely responsible for its role in treating DCI. Three other pharmacodynamic effects of lignocaine, membrane stabilisation, reduction in cerebral oxygen consumption and favourable haemodynamic properties in the ischaemic brain, increased cerebral blood flow and reductions in both intracranial and mean arterial pressure, may also contribute to its efficacy.[1]

In considering the value of any drug commonly used acutely, the pharmacokinetics of the agent are especially relevant. Lignocaine can, and indeed because of a significant first pass effect, needs to be given parenterally. The drug is metabolised with renal excretion of metabolites and dosage adjustment is not normally required, except in cases of major hepatic or renal dysfunction. A short half life (1-2 hours) means that a steady-state can be quickly achieved and, in the event of overdosage, cessation of infusion will be followed by a relatively rapid diminution in blood level and unwanted effects. Lignocaine has a narrow therapeutic index, but the therapeutic range is well established (6-21 μmol/l). Drewry and Gorman, in a single case report of its use as adjuvant therapy in DCI, showed benefit from lignocaine administered in doses sufficient to achieve plasma levels at the lower end of this range.[5] Mitchell, when reviewing the in vivo animal data, showed that in studies where doses higher than those considered to be within the normal anti-arrhythmic range were used benefit was not as great as that obtained from the use of conventional doses.[1]

The adverse effects of lignocaine are predominantly seen in the cardiovascular and central nervous systems and are well known. The properties of the other parenteral aminoethylamide local anaesthetic agents (e.g. bupivacaine, etidocaine, mepivacaine, prilocaine, ropivacaine) do not suggest a role for any of these in preference to lignocaine. Mexiletine, structurally related to lignocaine, and available in both parenteral and oral dosage forms, is the only orally available option but is very poorly tolerated and has no properties that suggest that it should be considered in preference to lignocaine.

Non-steroidal anti-inflammatory agents (NSAIDs)

If the anti-inflammatory effect of lignocaine is considered beneficial in DCI then it is not unreasonable to consider the use of other pharmacological agents that interrupt inflammatory pathways. Hallenbeck et al., using a dog model, have shown that the NSAID indomethacin, in combination with heparin and prostaglandin I_2, speeds cerebral neuronal recovery from a standardised ischaemic insult. The effect of any of the three agents used alone was not statistically significant.[4]

NSAIDs exert their anti-inflammatory effect by inhibition of cyclooxygenase which subsequently leads to inhibition of the synthesis of prostaglandins.[6] Cyclooxygenase inhibition causes reversible inhibition of platelet aggregation. The individual contributions of the anti-inflammatory and anti-platelet effects of NSAIDs to the overall effect of the agents in DCI have not yet been defined.

Inhibition of prostaglandins in the kidney and gastrointestinal mucosa is responsible for the well known adverse effects, in both organs, seen with NSAIDs.[7,8] Which agent to use is a reasonable question to ask, given that there are fifteen different NSAIDs in a wide variety of dosage forms available in Australia. The desire of pharmaceutical companies to have at least one of these widely prescribed agents in their inventory, and the fact that no one drug stands out as being significantly clinically superior, are two reasons for the multiplicity of agents on offer. In practice, patient preference often remains the final arbiter.

While some of the agents are locally irritant to the gastric mucosa, toxicity is principally mediated systemically. The dramatic decline in renal function from normal to acute renal failure in otherwise well relatively young patients presenting for elective surgery and receiving the parenteral NSAID ketorolac (Toradol®) either peri- or post-operatively, as an alternative to traditional narcotic analgesic agents highlights the dangers associated with the administration of NSAIDs at a time when renal circulation is stressed.[9] Applying the same analogy to otherwise fit divers presenting with symptoms of DCI, resuscitation and fluid repletion should be completed and baseline urea and creatinine measured before using a NSAID. Ongoing monitoring of renal function during treatment with a NSAID in this setting would be prudent.

Case control studies in UK populations have shown that there is a difference in the propensity for different NSAIDs to cause damage to the gastric mucosa. Longer acting NSAIDs, while popular because of the need to take the drug only once daily, appear more toxic than some of the older shorter acting agents.[10-12] Piroxicam (Feldene®) consistently compares unfavourably with ibuprofen (Brufen®) while agents such as naproxen (Naprosyn®) and diclofenac (Voltaren®) fit somewhere in the middle. Accepting that some of the difference in toxicity may be explained by not using equivalent anti-inflammatory doses, a case can still be made for starting patients on ibuprofen before moving on to longer acting agents in the event of lack of response.[13] While known risk factors for gastrointestinal bleeding associated with NSAID use, such as old age, smoking, history of peptic ulcer disease and the presence of cardiovascular disease, are unlikely to be present in the majority of those presenting with DCI, providing anti-inflammatory efficacy is not compromised, it is reasonable to start with a drug with less gastrointestinal toxicity.

New developments in NSAID research include the combination of a nitric oxide releasing moiety with

conventional NSAIDs. In animal studies these agents have demonstrated anti-inflammatory efficacy comparable to the NSAID alone with less gastrointestinal toxicity.[14] Cyclooxygenase (Cox) exists in vivo as two molecules (Cox-1 and Cox-2). Whereas Cox-1 is ubiquitous occurring in most tissues, Cox-2 is far more localised and is inducible at sites of inflammation. Conventional NSAIDs inhibit both isoenzymes to varying extents. Naproxen and diclofenac are relatively Cox-2 specific when compared with piroxicam, which is not, and this ranking is consistent with the greater gastrointestinal toxicity seen with the latter agent. Highly specific Cox-2 inhibitors have the potential to be safer agents and one such drug, meloxicam is currently undergoing clinical trials in Australia.[15]

If studies currently in progress provide further evidence for a role for lignocaine and NSAIDs as useful agents in the adjuvant treatment of DCI, then combination therapy using lignocaine and a NSAID may prove worthy of investigation. While in the acute setting of any illness, including DCI, the use of NSAIDs should be tempered with an appreciation of their potential to cause damage to an already stressed gastric mucosa and under-perfused kidney, lignocaine has an established role in the emergency treatment of ventricular arrhythmias. While lignocaine may be the preferred initial agent, if on-going anti-inflammatory medication is indicated oral NSAIDs may have a role to play. If this proves to be the case, which NSAID to use, out of a confusing array of agents which will only get larger, remains to be determined.

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