Concussion treatment

Should we treat concussion pharmacologically?

P McCrory

The need for evidence based pharmacological treatment for the concussed athlete

The medical management of concussion in sport has traditionally involved close observation and "masterly inactivity". With the use of clinical assessment and neuropsychological testing we have the ability to individualise patient management and determine safe and appropriate return to play strategies. At the present time, the sports physician has no evidence based pharmacological treatment to offer the concussed athlete. The ability to treat concussion with specific drug therapy requires an understanding of the pathophysiological changes that accompany concussive injuries.

PATHOPHYSIOLOGY OF SPORT RELATED CONCUSSION

Concussive brain injury has long been thought to evoke immediate and irreversible damage to the brain. While this may be true in moderate to severe traumatic brain injury, the evidence that this occurs in milder injuries such as concussion is not compelling. Recent experimental evidence suggests that the pathogenesis of axonal dysfunction resulting from head trauma is complex.[1]

In addition, studies of moderate to severe traumatic brain injury have revealed that a cascade of neurochemical, ionic, and metabolic changes occur following experimental brain injury.[2] The assumption is that similar changes occur in milder injury although this remains controversial. Most notably, an injury induced ionic flux across the cell membrane due to the release of the excitatory amino acids, has been shown to increase glycolysis that results in a state of metabolic depression due to a decrease in both glucose and oxidative metabolism accompanied by a decrease in cerebral blood flow.[2 3] Each element of this cascade has a different time window that may have important implications in treating concussed individuals.

TREATMENT OPTIONS

There are many pharmacological management options that have been proposed for all grades of brain injury. Readers are referred to some of the larger texts and recent reviews on these topics for more complete discussion.[4–7] The list below outlines some of the recent developments and areas where treatment may have a role. In many cases, the evidence is based upon studies of severe brain injury and readers need to interpret this in light of the discussion above. These treatments are summarised in table 1.

Corticosteroids

Corticosteroids have been utilised for many years in experimental neurotrauma, initially based upon their ability to stabilise lysosomal membranes and reduce tissue oedema. There are a number of studies that suggest both positive and negative benefits of using corticosteroids in severe brain injury.[8] Other steroid compounds, particularly the lazaroids or 21-amino steroids, that inhibit lipid peroxidation also have protective benefit in neurotrauma models. One such compound, tirilazad mesylate has been shown to improve behavioural recovery in mice.[9]

Free radical scavengers and antioxidants

Treatment with vitamin C or E, if administered pre-injury, has been shown to provide protection in various models of central nervous system (CNS) trauma where free radicals are generated.[10 11] Some concern however has been raised by the large epidemiological studies of antioxidant use for cardiovascular disease where antioxidant therapy was associated with an increase in cancer incidence. The mechanism for this in not known.

Drugs inhibiting arachidonic acid metabolism

Toxic breakdown products of arachidonic acid metabolism may exacerbate CNS injury. These include thromboxanes, peptidyl leukotrienes, and free radicals. Studies of cyclo-oxgenase inhibitors (for example, ibuprofen) and mixed cyclo-oxygenase-lipoxygenase inhibitors have shown therapeutic benefit in animal models of spinal cord injury.[12] No specific trials of this therapy have been performed with mild traumatic brain injury.

Drugs that modify monoamine function

There is a well documented sympathoadrenal response following traumatic brain injury, however, whether blocking this response has a therapeutic benefit is unknown. It has been known anecdotally since the Second World War, that cholinergic antagonists such as scopolamine can reduce the behavioural deficits following moderate to severe brain injury. A recent randomised trial however was terminated prematurely because of unacceptable psychomimetic side effects suggesting that this agent may not be a practical treatment option.[5]

Glutamate receptor antagonists

Increased extracellular levels of glutamate and aspartate correlate with brain injury severity in animal models.[13] Treatment with NMDA antagonists, AMPA antagonists, and magnesium have suggested a protective benefit in animal and limited human studies.[13] These agents may be of increasing importance once safety and other issues are dealt with.

Calcium channel antagonists

It has been proposed that the entry of calcium through voltage-dependent channels may contribute to secondary brain injury. Despite the intuitive logic of

Abbreviations: CNS, central nervous system; TRH, thyrotrophin releasing hormone

Table 1 Summary of treatment options

Treatments that are possibly effective	Treatments unlikely to be effective	Treatments that may place the athlete at risk of adverse events
Drugs inhibiting arachidonic acid metabolism	Neurotrophic factors	Free-radical scavengers
Calcium channel antagonists	TRH/TRH analogues	Antioxidants
Corticosteroids		Drugs that modify monoamine function
		Hyperbaric oxygen therapy

treatment with calcium channel antagonists, a number of randomised trials of various agents have failed to demonstrate protective benefit.[14 15] Recently a novel calcium channel agent, S-emopamil, has been shown to be beneficial in experimental injury.[16]

Opiate receptor antagonists

Endogenous opioids contribute to secondary damage following CNS trauma. Studies have suggested that the kappa opioid receptor or its isoforms may be significant in the modification of these injuries. Reanalysis of data from randomised trials of spinal cord injury have suggested a benefit from naloxone although the dose studied may have been too high.[17 18]

TRH and TRH analogues

Thyrotrophin releasing hormone (TRH) was initially used in the treatment of acute spinal cord injury because of its ability to antagonise many of the actions of endogenous opioids. This agent may also have effects on platelet function, leukotriene activation, and excitatory amino acid release. Protective effects in CNS injury are dose-related and are found even when treatment is delayed up to 24 hours.[19 20]

Neurotrophic factors

The ability of injured neurons in the adult brain to recover from injury depends on the expression of growth related genes and the responsiveness to survival and growth signals in the environment.

Nerve growth factor: The neuroprotective efficacy of intracerebral nerve growth factor infusion has been demonstrated during the acute phase of experimental head injury. This beneficial effect of nerve growth factor may be related to its ability to attenuate traumatically induced apoptotic cell death.[21]

Insulin-like growth factor-1: Intravenous insulin-like growth factor-1 has been evaluated for the treatment of moderate to severe head injury in a phase II safety and efficacy trial.[22]

Bcl-2: This proto-oncogene has actions similar to those of brain-derived neurotrophic factor in promoting the regeneration of severed CNS axons in the mammalian CNS.[23] The mode of this action is likely via extracellular signalling pathways that are involved in both neuronal survival and axon elongation.

Hypothermia

Significant morbidity and mortality of patients with traumatic brain injury is associated with post-traumatic inflammatory complications. Hypothermia has been suggested as a treatment to lessen these inflammatory reactions. Hypothermia, applied immediately after severe traumatic brain injury, reduces the post traumatic increase in interleukin-1 beta-mediated nerve growth factor production.[24] Thus, hypothermia, while reducing the inflammatory response, may also hinder the brain's intrinsic repair mechanism. In phase 1 and phase 2 trials, short (<48 hours) periods of moderate (32–33°C) hypothermia are well tolerated and provide limited evidence of a beneficial effect on the outcome following moderate to severe traumatic brain injury. Phase 3 randomised controlled trials are currently underway.[4]

Hyperbaric oxygen therapy

The delivery of high concentrations of oxygen under pressure has been proposed as a means of enhancing cerebral oxygenation and hence injury recovery post-injury. Possible mechanisms of action include cerebral vasoconstriction, improvement in glucose metabolism and reduction of cerebral oedema. Hyperbaric oxygen may also have a potentially harmful effect on the injured brain by supplying oxygen for free radical reactions that result in iron-catalysed lipid peroxidation. In severe brain injuries, randomised trials have demonstrated an improved mortality rate with hyperbaric therapy however there was no improvement in functional outcome at 12 months.[25]

OTHER TREATMENT STRATEGIES

There are a number of other agents that have been utilised either in small clinical trials, experimental studies or reported anecdotally to be of benefit. Agents such as anion transport inhibitors[26] and cytokines[5] have been proposed as well as combination therapy directed at a number of elements of the injury cascade.[27] Even nutritional supplements, such as creatine, have been proposed to be of benefit in severe traumatic brain injury.[28] Further randomised controlled trials are necessary with all these agents prior to consideration or their recommendation for widespread clinical use.

CONCLUSION

In summary, at the present time the clinician has no evidence based pharmacological treatment to offer the concussed athlete. Although as physicians we often feel the need to treat "something" rather than sit idly by and observe the clinical state, it is critical that we bear in mind the Hippocratic aphorism *"Primum non nocere"*. And to paraphrase Hippocrates further; Life is short, the art is long, opportunity fleeting, experience deceiving, and judgment difficult. Thus medicine was almost three millennia ago and remains true today.

Br J Sports Med 2002;**36**:3–5

Author's affiliation

P McCrory, Centre for Sports Medicine Research & Education and Brain Research Institute, University of Melbourne, Melbourne, Australia 3004

Correspondence to: Dr P McCrory, PO Box 93, Shoreham, Vic 3916, Australia; pmccrory@compuserve.com

REFERENCES

1 **Povishlok J**, Pettus E. Traumatically induced axonal damage: evidence for enduring changes in axolemmal permeability with associated cytoskeletal change. *Acta Neurochir Suppl* 1996;**66**:81–6.
2 **Hovda D**, Lee S, Smith M, *et al*. The neurochemical and metabolic cascade following brain injury: moving from animal models to man. *J Neurotrauma* 1995;**12**:903–6.
3 **Takayama Y**, Maeda T, Koshinaga K. Role of excitatory amino acids-mediated ionic fluxes in traumatic brain injury. *Brain Pathol* 1995;**5**:427–35.
4 **Narayan R**, Wilberger J, Povishlok J. *Neurotrauma*. New York: McGraw-Hill, 1996.
5 **McIntosh T**. Novel pharmacological therapies in the treatment of experimental traumatic brain injury: a review. *J Neurotrauma* 1993;**10**:215–61.
6 **McCrory P**, Johnston K, Meeuwisse W, *et al*. Evidence based review of sport related concussion—basic science. *Clin J Sport Med* 2001;**11**:160–6.
7 **Johnston K**, McCrory P, Mohtadi N, *et al*. Evidence based review of sport-related concussion—clinical science. *Clin J Sport Med* 2001;**11**:150–60.
8 **Braughler J**, Hall E. High dose methyl prednisolone and CNS injury. *J Neurosurg* 1988;**64**:985–6.
9 **Hall E**, Yonkers P, McCall J, *et al*. Effect of the 21-amino steroid U-74006F on experimental head injury in mice. *J Neurosurg* 1988;**68**:456–61.
10 **Clifton G**, Lyeth B, Jenkins L. Effect of D1 alpha tocepherol succinate and polyethelene glycol on performance tests after fluid percussion brain injury. *J Neurotrauma* 1989;**6**:71–81.
11 **Yoshida S**, Busto R, Ginsberg M. Compression induced brain edema: modificaion by prior depletion and supplementation of vitamin E. *Neurology* 1983;**33**:166–72.
12 **Hallenbeck J**, Jacobs T, Faden A. Combined PGI2, indomethacin and heparin improves neurological recovery after spinal trauma in cats. *J Neurosurg* 1983;**58**:749–54.
13 **Nilsson P**, Hillered L, Ponten U, *et al*. Changes incortical extracellular levels of energy related metabolites and amino acids following concussive brain injury in rats. *J Cereb Blood Flow Metab* 1990;**10**:631–7.
14 **Teasdale G**. A randomised trial of nimodipine in severe head injury. *J Neurotrauma* 1991;**9**:S545–50.
15 **Compton J**, Lee T, Jones N. A double blind placebo controlled trial of the calcium entry blocking drug nicardipine in the treatment of vasospasm following severe head injury. *Br J Neurosurg* 1990;**4**:9–16.
16 **Okiyama K**, Rosenkrantz TS, Smith DH, *et al*. (S)-emopamil attenuates acute reduction in regional cerebral blood flow following experimental brain injury. *J Neurotrauma* 1994;**11**:83–95.
17 **Bracken M**, Holford T. Effects of timing of methyl prednisolone or naloxone administration on recovery of segmental and long tract neurological function in NASCIS2. *J Neurosurg* 1993;**79**:500–7.
18 **Bracken M**, Shepard M, Collins W. A randomised controlled trial of methylprednisolone or naloxone in the treatment of acute spinal cord injury. *New Eng J Med* 1990;**322**:1405–11.

19 **Faden A**, Jacobs T, Smith M. TRH in experimental spinal cord injury. *Neurology* 1984;**34**:1280–4.
20 **McIntosh T**, Fernyak S, Hayes R, *et al*. Beneficial effect of the non-selective opiate antagonist naloxone hydrochloride and the TRH analogue YM-14673 on long-term neurobehavioural outcome following experimental brain injury in the rat. *J Neurotrauma* 1993;**10**:373–84.
21 **Sinson G**, Perri B, Trojanowski J, *et al*. Improvement of cognitive deficits and decreased cholinergic neuronal cell loss and apoptotic cell death following neurotrophin infusion after experimental traumatic brain injury. *J Neurosurg* 1997;**86**:511–18.
22 **Hatton J**, Rapp R, Kudsk K. Intravenous insulin-like growth factor-1 (IGF-1) in moderate-to-severe head injury: a phase II safety and efficacy trial. *J Neurosurg* 1997;**86**:779–86.
23 **Chen D**, Schneider G, Martinou J, *et al*. Bcl-2 promotes regeneration of severed axons in the mammalian CNS. *Science* 1997;**385**: 434–9.
24 **Goss J**, Styren S, Miller P. Hypothermia accentuates the normal increase in interleukin 1 beta RNA and nerve growth factor following traumatic brain injury in the rat. *J Neurotrauma* 1995;**12**: 159–67.
25 **Rockswold G**, Ford S, Anderson D. Results of a prospective randomised trial for the treatment of severely brain injured patients with hyperbaric oxygen. *J Neurosurg* 1992;**76**:929–34.
26 **Kimelberg H**, Cragoe E, LR N. Improved recovery from a traumatic-hypoxic brain injury in cats by intracisternal injection of an anion transport inhibitor. *CNS Trauma* 1987;**4**:3–14.
27 **Faden A**. Comparison of single versus combination drug strategies in experimental brain trauma. *J Neurotrauma* 1993;**10**:91–100.
28 **Sullivan P**. Dietary supplement creatine protects against traumatic brain injury. *Ann Neurol* 2000;**48**:723–9.

EDUCATION PROGRAMME

British Association of Sport and Exercise Medicine in association with the National Sports Medicine Institute

Education programme 2002

Intermediate Sports Injury Management and Medicine—Head, Neck, & Upper Limb
Lilleshall National Sports Centre, 17–22 February.

General Sports Medicine
Lilleshall National Sports Centre, 21–26 April.

Diploma Preparation
Sheffield Centre of Sports Medicine, April–May.

Current Concepts: Lower Limb Rehabilitation
DSMRC Headley Court, Surrey, 10–11 May .

Intermediate Sports Injury Management and Medicine—Lumbar Spine, Thorax, Groin, Pelvis, & Hip
Lilleshall National Sports Centre, 7–12 July .

General Sports Medicine
Lilleshall National Sports Centre, 22–27 September.

Practical Sport and Medicine Meeting
Club La Santa, Lanzarote (families & non-delegates welcome; deadline 17 July, 2002), 3–10 October.

Diploma Preparation
Location and date to be confirmed, October.

The Queen's Golden Jubilee & Post Commonwealth Games BASEM Congress
The Low Wood Hotel and Conference Centre, Windermere, 10–13 October.

Intermediate Sports Injury Management and Medicine—Lower Limb
Lilleshall National Sports Centre, 17–22 November.

Current Concepts
Topic, location, and date to be confirmed, December.

Education programme 2003

Intermediate Sports Injury Management and Medicine—Head, Neck, and Upper Limb
Lilleshall National Sports Centre, 16–21 February.

General Sports Medicine
Lilleshall National Sports Centre, 27 April–2 May.

The Cutting Edge
Sheffield, 3–7 September
(Contact: r.m.bartlett@shu.ac.uk)

For further details of these courses please contact Mr Barry Hill, The National Sports Medicine Institute, 32 Devonshire Street, London W1G 6PX, UK. Tel: 020 7486 3974; Fax:020 7935 0402; email: barry.hill@nsmi.org.uk; www.nsmi.org.uk