Pharmacological Treatment of Head Injury

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INTRODUCTION

Although treatment of primary brain damage is theoretically possible, to date most pharmacological treatment of head injury has been based on the prevention and treatment of secondary brain damage. This review concentrates on the pharmacological treatment of secondary brain damage caused by **ISCHAEMIA** and does not set out to address the prophylaxis and treatment of secondary infection. Much of the experimental work has been encouraging and "pharmacological neuroprotection" has been clearly demonstrated in animal models of head injury and stroke. Disappointingly, many of the clinical studies have failed to demonstrate the benefits that were expected to translate from this animal work. There may be several reasons for this: animal studies are very precise in carefully controlled subjects with uniform lesions. By contrast, human head injury represents a vast spectrum of different conditions with differing pathophysiology. Perhaps one of the mistakes that has been made with clinical trials in head injury has been to include all types of lesions in patients with different clinical features. Also, we may have been mistaken in expecting to demonstrate significant beneficial effects in these patients irrespective of the severity of injury. This is asking a lot of our relatively crude outcome measures. A further problem arises from the uncertainty of the therapeutic time window in human head injury and in clinical trials neuroprotective agents may have been administered too late. Finally, species differences may account for the lack of effect of these drugs in human head injury and stroke.

Nevertheless, it is an undisputed fact that more than 80 percent of patients with head injury who die have ischaemic neuronal damage [IND] at autopsy [1,2]. Also, it is now recognized that this occurs during life if cerebral blood flow (CBF) is measured in the early hours after head injury (Zauner, 1996 #1243). It is therefore relevant to explore these neuroprotective strategies in head injured patients because there is the expectation that some of the IND in the penumbra could be prevented.

NATURE OF ISCHAEMIC NEURONAL DAMAGE IN HEAD INJURY

Ischaemia neuronal damage may be global or focal. Global IND may be associated with a reduction in cerebral perfusion pressure [CPP], either due to a fall in blood pressure or a rise in intracranial pressure [ICP]. Effective monitoring and treatment may reduce the effects of the secondary CPP reductions that are so common following human head injury (Jones, 1994 #11404). These aspects of head injury management are dealt with elsewhere in this volume [3,4]. Suffice it to say that low CPP causes boundary zone infarction in the watershed zones of the vascular territories between the anterior, middle and posterior cerebral arteries (figure 1). Hypoxia from its various causes may

Table 1: The effect of extracranial insults on the outcome from head injury[5-8]

	Poor outcome (%) with and without extracranial insults			
	Kohi *et al*. (1984)	Gentleman & Jennett (1981)	Miller & Becker(1982)	Chesnut *et al* (1993)
Hypoxia and hypotension	100	100		94
Hypotension alone	88	75	65	74
Hypoxia alone	71	59	65	55
Neither insult	27	34	36	49

also produce boundary zone infarction. The combination of hypoxia and hypotension is particularly dangerous as has now been well documented clinically (Table 1)[5-7](Chesnut, 1993 #1033).

FOCAL ISCHAEMIA NEURONAL DAMAGE

Focal IND may be due to primary large vessel injury, secondary large vessel compression or compression / neurotoxicity in relation to a traumatic haematoma.

Focal infarction from injury to the internal carotid artery or to the middle cerebral artery is well documented[9] (figure 2). Tentorial herniation may compress the posterior cerebral artery and, if unrelieved, may lead to medial occipital infarction (figure 3). The third (and most common) mechanism of production of focal IND is in relation to haematomas. Early experimental work demonstrated that there is a large area of ischaemia around a haematoma[10] [11] and that this is analogous to the core and penumbra seen with focal infarction produced by middle cerebral artery occlusion (MCAO). Therefore any neuroprotective drugs that reduce IND from MCAO might also be capable of salvaging the penumbra around a haematoma. The same arguments apply to surface haematomas (subdural and epidural) [12] which have been shown to produce ischaemia of the underlying compressed cortex. The question is whether or not these pharmacological strategies can be translated into human head injury.

PHARMACOLOGICAL STRATEGIES

The cell membrane and its ionic pump and electrolyte channels are responsible for maintaining ionic and electrical stability. Ischaemia induces a chain of events leading to activation of voltage operated and receptor operated calcium channels. The influx of calcium into the cells leads to a series of initially reversible but later irreversible processes, which will culminate in the death of the cell. This so-called "Ischaemic cascade" is triggered by the release of glutamate and other excitotoxic amino acids, which act at a number of sites on the postsynaptic membrane. These include 2-amino-3 hydroxy-5 methyl isoxazole-4 propionic acid (AMPA), N-Methyl-D-Aspartate (NMDA) and metabotropic receptors, which effect membrane depolarisation, calcium influx and release of calcium from intracellular stores. Subsequent enzyme activation and release of free radicals damages the phospholipid bilayer of the cell membrane thus disrupting the cytoskeletal architecture.

Steroids help to preserve the stability of the phospholipid bilayer and this has been the rationale behind their use in human head injury. The steroids used include dexamethasone, high dose glucocorticoids and the 21-aminosteroids. Calcium antagonists such as Nimodipine can block calcium influx through the voltage-operated channels. Influx of

calcium through the NMDA receptor can be blocked by the physiological calcium channel blocker magnesium or by non-competitive NMDA receptor antagonists like MK-801. Competitive NMDA receptor antagonists include D-CPP-ene which reacts at the glutamate recognition site. Glycine upregulates the NMDA receptor and antagonists acting at this site may also limit calcium influx.

CLINICAL TRIALS IN HEAD INJURY:

1. Steroids: Many of the early phase III clinical trials in head injury utilized dexamethasone. However, meta-analysis of these studies has shown that significant beneficial effect is unlikely, and if present would be small (1-2 percent) [13]. Nevertheless, a large prospective randomised controlled trial of methylprednisolone within 8 hours of head injury is currently in progress (The CRASH Trial). Phase III studies of the 21-aminosteroid Tirilazad, which is a free radical scavenger, have not demonstrated any benefit from treatment [14].

2. Calcium Antagonists: There have been 2 large trials of the calcium antagonists Nimodipine in head injury. Both trials failed to show a benefit from treatment [15] (Group, 1994 #536), although subgroup analysis has shown that patients with traumatic subarachnoid haemorrhage [SAH] fared better. A subsequent small trial in patients with traumatic SAH has shown that Nimodipine significantly improves outcome [16]. A further large trial in patients with traumatic SAH may confirm this finding.

3. Glutamate Antagonists: Several large phase III trials of glutamate antagonists in head injury have failed to confirm the encouraging results from animal studies (Table 2). So far, all of these trials have shown no difference between drug and placebo when the primary endpoint of Favorable compared with Unfavorable outcome has been measured using the Glasgow Outcome Scale. Some of these studies, however, have indicated that early treatment (within 4 to 6 hours) may be more promising. Also they may be more effective in focal injury than in diffuse injury.

4. Cannabinoids: Most recently Cannabinoid substances (derived from naturally occurring plants) have been shown to antagonise both the voltage and receptor operated calcium channels. These plant-derived drugs are also potent free radical scavengers. Phase II studies of Dexanabinol in human head injury are underway.

Other possible avenues of pharmacological treatment include the use of immunosuppressive agents like cyclosporin and other newer derivatives. Once brain damage has taken place, repair and regeneration may be accelerated by a variety of new agents which stimulate nerve and axonal growth: for example Nerve Growth Factor and other Growth Factors have shown promise in experimental studies.

Table 2: Clinical trials of glutamate antagonists in head injury (modified from Teasdale and Bannon – 1997)[17]

Class	Drug	Company	Results
Presynaptic release inhibition	619C89	Glaxo/Wellcome	Phase II trial stopped
Postsynaptic Competitive:	CGS19755	Ciba/Geigy	Phase III trial stopped
	D-CPP-ene	Novartis	Phase III – no benefit
Postsynaptic Non competitive:	Aptiganel H	Cambridge Neuroscience Boehringer	Phase III in progress
Polyamine site	Eliprodil	Synthelabo	Phase III – no benefit

FUTURE CLINICAL TRIALS

Future trials should address the problems arising from the heterogeneity of human head injury and should focus on specific subgroups of head injured patients that have been identified from previous clinical studies. As indicated above such subgroups may include SAH, focal intracerebral haemorrhage, contusions and focal ischaemic damage. Both clinicians and the pharmaceutical industry should realise that treatment may have to be given very early after head injury to optimise potential beneficial effects. The role of steroids in primary diffuse axonal injury remains to be clarified. Similarly the treatment of primary contusions may offer an opportunity to prevent or reverse the ischaemic cascade if such neuroprotective drugs are given very early, perhaps even at the roadside.

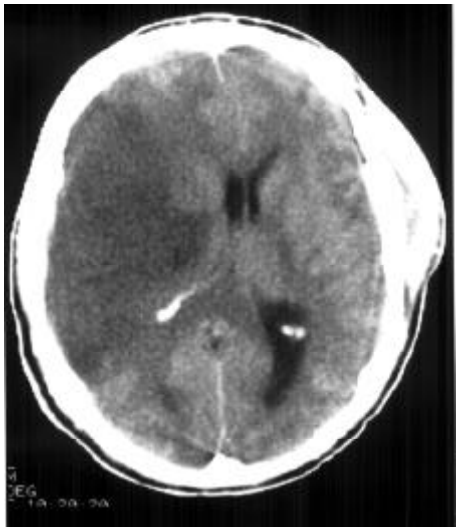

Figure 2: CT scan from a patient with a left hemiplegia following a right cervical carotid injury from a safety belt (note the left frontal scalp contusion caused by rotational impact with the steering wheel).

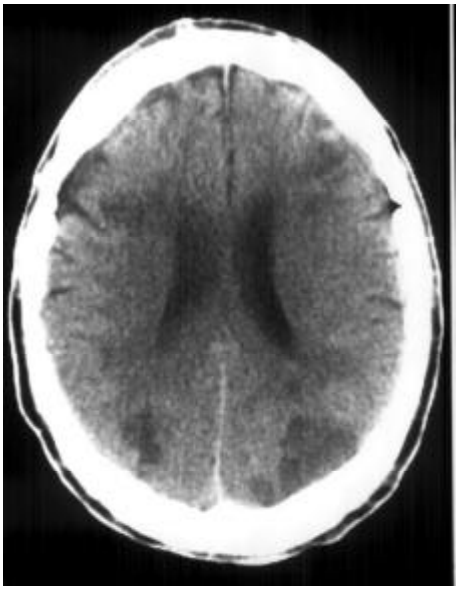

Figure 1: CT scan from a patient 2 weeks after a global hypoxic and ischaemic insult associated with severe head injury: bilateral boundary zone infarcts are seen anteriorly and posteriorly.

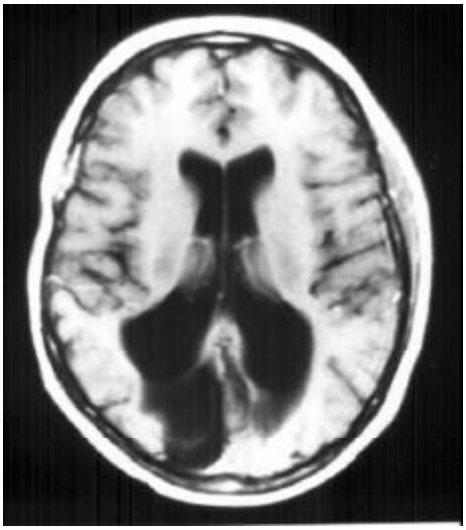

Figure 3: MRI from a patient 6 months after a head injury with late relief of a right tentorial hernia with compression of the right posterior cerebral artery: a right medial occipital infarct has developed.

REFERENCES:

1. Graham DI, Adams JH, Doyle D. Ischaemic brain damage in fatal non-missile head injuries. Journal of Neurological Sciences 1978;39:213-234.
2. Graham DI, Ford I, Adams JH, Doyle D, Teasdale GM, Lawrence AE, et al. Ischaemic brain damage is still common in fatal non-missile head injury. Journal of Neurology Neurosurgery and Psychiatry 1989;53:346-350.
3. Chambers I, Mendelow A. Monitoring the head injured patient. EMN proceedings 1999:(In Press).
4. Robertson C. Trial of ICP/CPP management in head injury. EMN Proceedings 1999:(In Press).
5. Kohi YM, Mendelow AD, Teasdale GM, Allardice GM. Extracranial insults and outcome in patients with acute head injury - relationship to the Glasgow Coma Scale. Injury 1984;16:25-29.
6. Gentleman D, Mendelow AD. Intracranial rupture of a pressure monitoring transducer: technical note. Neurosurgery 1986;19:91-92.
7. Miller JD, Becker DP. Secondary insults to the injured brain. Journal of the Royal College of Surgeons of Edinburgh 1982;27(5):292-298.
8. Chesnut R, Marshall L, Klauber M, al. e. The role of secondary brain injury in determining outcome from severe head injury. J Trauma 1993;34:216 - 222.
9. Ueda T, Kikuchi H. Traumatic stenosis of the internal carotid artery in children. Surgical Neurology 1986;26:368.
10. Mendelow AD, Bullock R, Teasdale GM, Graham DI, McCulloch J. Intracranial haemorrhage induced at arterial pressure in the rat: Part 2. Short term changes in local cerebral blood flow measured by autoradiography. Neurol. Res. 1984;6:189-193.
11. Nehls DG, Mendelow AD, Graham DI, Teasdale GM. Experimental intracerebral hemorrhage - early removal of a spontaneous mass lesion improves late outcome. Neurosurgery 1990:674-682.
12. Bullock R, McCulloch J. Focal ischaemic damage is reduced by CPP-ene. Studies in 2 animal models. Stroke 1990;21(Suppl. III):32.
13. Roberts I. Steroids in head injury. Br Med J 1998;?:?
14. Marshall LF, Marshall SB. Pitfalls and advances from the international tirilazad trial in moderate and severe head injury. J Neurotrauma 1996;12(929 - 932).
15. Bailey I, Bell BA, Gray J, Gullan R, Heiskannen U, Marks PV, et al. The effect of Nimodipine on outcome after head injury: a prospective randomised control trial: Springer Verlag, 1991.
16. Kakarieka A, Braakman R, Schakel E. Clinical significance of the finding of subarachnoid blood on CT scan after head injury. Acta Neurochirurgica 1994;129:1 - 5.
17. Teasdale G, Bannan P. Neuroprotection in head injury. In: Reilly P, Bullock R, editors. Head Injury. Pathophysiology and management of severe closed injury. London: Chapman and Hall, 1997:423 - 438.

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