

Pharmacology of Traumatic Brain Injury: Where Is the “Golden Bullet”?

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Traumatic brain injury (TBI) represents a major health care problem and a significant socioeconomic challenge worldwide. In the United States alone, approximately 1.5 million patients are affected each year, and the mortality of severe TBI remains as high as 35%–40%. These statistics underline the urgent need for efficient treatment modalities to improve posttraumatic morbidity and mortality. Despite advances in basic and clinical research as well as improved neurological intensive care in recent years, no specific pharmacological therapy for TBI is available that would improve the outcome of these patients. Understanding of the cellular and molecular mechanisms underlying the pathophysiological events after TBI has resulted in the identification of new potential therapeutic targets. Nevertheless, the extrapolation from basic research data to clinical application in TBI patients has invariably failed, and results from prospective clinical trials are disappointing. We review the published prospective clinical trials on pharmacological treatment modalities for TBI patients and outline future promising therapeutic avenues in the field.

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INTRODUCTION

Traumatic brain injury (TBI) is the leading cause of death and disability in young people (1,2). Despite advances in research and improved neurological intensive care in recent years, the clinical outcome of severely head-injured patients is still poor. Evaluation of direct and indirect costs reveals that TBI is a 60 billion dollar “industry” in the United States (3–6). Posttraumatic brain damage is determined by a combination of primary and secondary insults. Primary damage results from mechanical forces applied to the skull and brain at the time of impact, leading to focal or diffuse brain injury patterns. In contrast to the

primary insult, secondary brain injuries evolve over time. These are characterized by a complex cascade of molecular and biochemical events that lead to neuroinflammation, brain edema, and delayed neuronal death. Early hypoxia and hypotension induce and perpetuate cerebral ischemia and reperfusion injuries and are independent predictors of adverse outcome after TBI (7) (Figure 1).

In the past decade, our understanding of the cellular and molecular changes that occur after TBI has significantly increased. A number of new potential therapeutic targets have been identified that may enable prevention of the onset or reduction of the extent of secondary

brain injuries. The evidence-based guidelines for the treatment of TBI patients were recently published in revised form by the Brain Trauma Foundation (8). Interestingly, most recommendations in these published guidelines are based on class II or III evidence, owing to a persistent lack of class I evidence-based data on treatment strategies for TBI (8). No specific pharmacological therapy is currently available that prevents the development of secondary brain injuries, and most therapeutic strategies have failed in translation from “bench to bedside.” We present a review of the current literature on prospective clinical trials of pharmacological treatment modalities in TBI patients.

METHODS

Comprehensive online literature searches were performed using the indexed databases MEDLINE/PubMed and the Cochrane Library. The primary intention of these searches was to identify prospective randomized controlled

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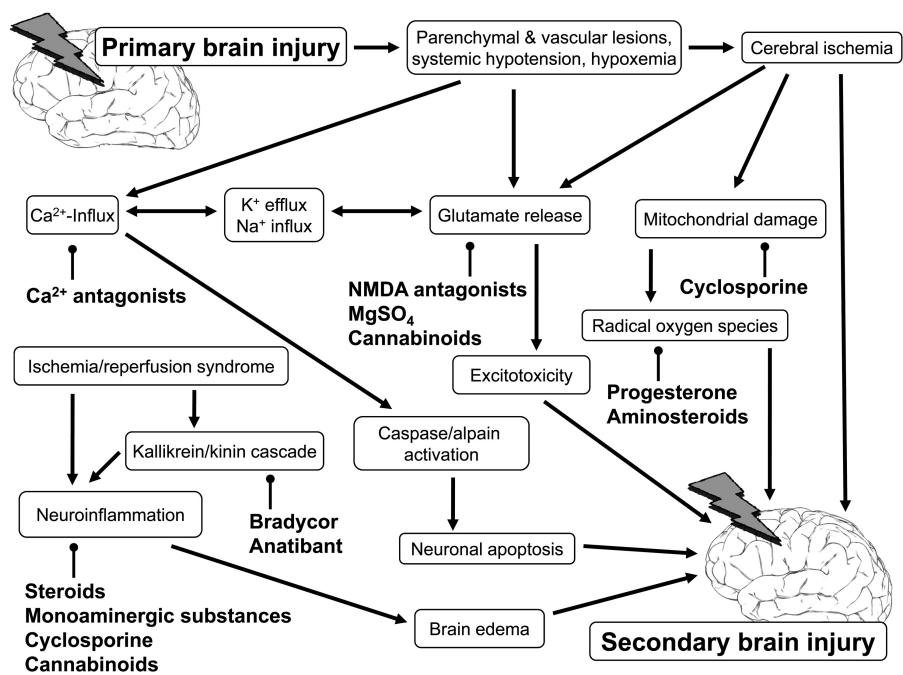


Figure 1. Pathophysiological mechanisms of secondary brain injury and selected points of action of pharmacological compounds discussed in this review. See text for details and explanations.

trials (RCTs), nonrandomized controlled trials (NRCTs), and published systematic reviews. Medical Subject Heading (MeSH) thesaurus keywords were applied as a standardized use of language to unify differences in terminology (Table 1). Appropriate MeSH headings and subheadings for each question were selected and modified on the basis of search results. Searches were limited to human studies, but not to sex or age. Original publications were evaluated for abstracts that were deemed relevant. If an acceptable systematic review or metaanalysis was identified, searches to update the data were typically limited to the time period following the search cutoff date reported in the review. Pharmacological agents were selected for analysis based on the operational strategy of positive yields on the literature searches (MEDLINE/PubMed) using the restriction of human pharmacological trials in head injury (RCTs and NRCTs) and systematic meta-analyses (Cochrane and MEDLINE/PubMed) published in the last 20 years,

from September 1, 1988 to July 1, 2008. This defined search led to the following pharmacological agents of interest, which are described in the present paper, steroids and steroid derivatives, N-methyl-D-aspartate (NMDA) receptor antagonists, endocannabinoids, monoaminergic substances, cyclosporine, calcium-channel blockers, and modulators of the kinin/kallikrein system (Table 1). The last online search was updated on July 1, 2008.

STERIODS

Corticosteroids: A “CRASH” Landing in TBI

The problem of extrapolating knowledge derived from experimental studies from bench to bedside with regard to pharmacological strategies in TBI is most explicitly exemplified by the role of steroids. Corticosteroids were introduced in the early 1960s as a treatment for brain edema. The administration of glucocorticoids in patients with brain tumors re-

sulted in marked clinical improvement, and glucocorticoids were found to be beneficial when administered in the perioperative phase of intracranial tumor surgery. Steroids became commonplace in the treatment of TBI in the 1970s owing to assumed beneficial effects when used in high doses (9,10). However, multiple clinical studies from the 1980s and 1990s were not able to provide definitive proof of a beneficial effect of steroids in TBI patients. This lack of adequate scientific knowledge led to the design of the largest clinical trial on head injury, aimed at prospectively recruiting 20,000 patients. This large-scale Corticosteroid Randomization after Significant Head Injury (CRASH) trial, a prospective, randomized, placebo-controlled multicenter trial, was designed to determine with high scientific accuracy whether there is a potential benefit of administering high-dose methylprednisolone in TBI patients (11). The CRASH trial had to be aborted, however, after enrollment of just 50% of the patients (n = 10,008), because of the finding of an unexpected increased mortality in head-injured patients treated with corticosteroids (11). The authors reported that the “verum” cohort of high-dose methylprednisolone (n = 5007) had a significantly increased mortality compared with the placebo control group (n = 5001) during the first 14 d after trauma (21.1% versus 17.9%, *P* < 0.001) (11). These shocking results indicated that the “pan”-inhibition of the immune response by the use of high-dose steroids is too broad and nonspecific for controlling posttraumatic inflammation. The negative results from the CRASH trial led to a highly provocative editorial in *The Lancet*, suggesting that the uncritical, anecdotal administration of corticosteroids to head-injured patients may have caused more than 10,000 deaths during the 1980s and earlier (12). The 1:1 extrapolation of these negative data from the CRASH trial must be judged cautiously, however, owing to some weaknesses in the study design. Nevertheless, current TBI treatment recommendations do not include the use of steroids, which

Table 1. Medical subject heading (MeSH) thesaurus keywords used for online literature searches in PubMed and Cochrane databases. The last online search was performed on 07/01/2008.

Compound	MeSH-Terms
Cannabinoids	"Traumatic Brain Injury" OR "Closed Head Injury" OR "Brain Injury" OR "TBI" OR "Brain Damage" AND "Endocannabinoids" OR "Dexabinol" OR "Cannabinoids" OR "Anandamide"
Glutamate (NMDA) Receptor Antagonists	"Traumatic Brain Injury" OR "Closed Head Injury" OR "Brain Injury" OR "TBI" OR "Brain Damage" AND "EAA" OR "Excitatory Amino Acid" OR "Neuroprotective Agent" OR "NMDA" OR "N-Methyl-D-Aspartate"
Magnesium sulfate (MgSO ₄)	"Traumatic Brain Injury" OR "Closed Head Injury" OR "Brain Injury" OR "TBI" OR "Brain Damage" AND "Magnesium-Chloride" OR "Magnesium Compounds" OR "Magnesium" OR "Magnesiumsulfate"
Corticosteroids	"Traumatic Brain Injury" OR "Closed Head Injury" OR "Brain Injury" OR "TBI" OR "Brain Damage" AND "Steroids" OR "Glucocorticoids" OR "Corticosteroids" OR "Cortisone" OR "Prednisolone" OR "Dexamethasone" OR "Methylprednisolone"
Aminosteroids	"Traumatic Brain Injury" OR "Closed Head Injury" OR "Brain Injury" OR "TBI" OR "Brain Damage" AND "Aminosteroids" OR "Tirilazad" OR "Lazaroid"
Progesterone	"Traumatic Brain Injury" OR "Closed Head Injury" OR "Brain Injury" OR "TBI" OR "Brain Damage" AND "Progesterone" OR "Sexual Hormones"
Monoaminergic substances	"Traumatic Brain Injury" OR "Closed Head Injury" OR "Brain Injury" OR "TBI" OR "Brain Damage" AND "Amphetamine" OR "Dopamine" OR "Methylphenidate" OR "Dextroamphetamine"
Cyclosporine	"Traumatic Brain Injury" OR "Closed Head Injury" OR "Brain Injury" OR "TBI" OR "Brain Damage" AND "Cyclosporine" OR "Immunosuppressant" OR "Cyclosporine A" OR "CsA"
Ca-Channel Blockers	"Traumatic Brain Injury" OR "Closed Head Injury" OR "Brain Injury" OR "TBI" OR "Brain Damage" AND "Calcium Channel Blocker" OR "Calcium Antagonist" OR "Nifedipine" OR "Verapamil" OR "Nifedipine" OR "Nimodipine" OR "Amlodipine" OR "Felodipine" OR "Diltiazem"
Inflammatory Modulators	"Traumatic Brain Injury" OR "Closed Head Injury" OR "Brain Injury" OR "TBI" OR "Brain Damage" AND "Kallikrein-Kinin" OR "Bradykinine Receptor Antagonists" OR "Kinins" OR "Bradycor" OR "Anatibant"

are considered obsolete and potentially harmful for the patient (13).

Aminosteroids

Lipid peroxidation is the free-radical-mediated formation of lipid peroxides. Once initiated, peroxidation is considered to be a self-propagating process that leads to cell membrane damage and cell death (14). Oxygen radical formation and lipid peroxidation start early after TBI and lead to ischemia and hypoxia. Free radicals in TBI are generated by mitochondrial damage (15–20). Tirilazad mesylate is a 21-aminosteroid that has been shown to inhibit lipid peroxidation in experimental animals (14). Tirilazad mesylate penetrates the intact blood-brain-barrier poorly but has a strong affinity for the vascular endothelium

(21). One randomized clinical study investigating the effect of tirilazad mesylate in the setting of TBI has been reported (22). This study enrolled 1120 patients with moderate (15%) to severe (85%) TBI. Patients received tirilazad mesylate or placebo every 6 h for a period of 5 d. Primary outcomes were mortality and Glasgow Outcome Scale (GOS) 6 months after TBI. There were no significant differences in either category at 6 months after injury. Subgroup analysis suggested that tirilazad mesylate may be effective in reducing mortality rates in males suffering from severe head injury with accompanying traumatic subarachnoid hemorrhage.

In a Cochrane Review, Roberts (23) calculated the risk of death in patients treated with tirilazad mesylate in a

United States trial reported by Marshall *et al.* The risk of death in patients given tirilazad mesylate was nearly identical to that in patients given placebo, relative risk (RR) = 1.05 (95% confidence interval [CI] 0.86 to 1.29). The risk of disability in patients treated with tirilazad mesylate was also almost identical to the risk in patients given placebo, RR = 1.07 (95% CI 0.93 to 1.23). These results indicate that there is no evidence to support the routine use of aminosteroids in the management of TBI. Future studies should investigate titration of the optimal time-window of drug delivery, a variable that appears to be crucial for potential beneficial effects in TBI patients. Administering the agent only in the first 7 d after injury may miss the optimal treatment period, thus leading to inaccurate assessment of

potential treatment benefits. One can argue that the antioxidants are potentially beneficial when they are present at the site and time of reactive oxygen species (ROS) formation. Because of the short half-life of these ROS, however, the drug may just miss the target.

Progesterone

A substantial amount of data indicate that progesterone, a gonadal hormone and neurosteroid naturally distributed in human brains, has potent neuroprotective properties (24,25). In animal studies, progesterone reduced cerebral edema, neuronal loss, and behavioral deficits by inhibiting secondary injury cascade (26–32). This finding led to further investigation in phase I and II clinical studies. Phase I, a single-center, double-blinded study, showed that stable progesterone levels could be achieved rapidly and safely by use of a two-phase intravenous infusion following TBI (33). Recently, results of the ProTECT (Progesterone for Traumatic Brain Injury, Experimental Clinical Treatment) study were published (34). In this phase II, single-center, double-blinded, placebo-controlled clinical pilot study, the safety and potential benefit of progesterone administration to patients with TBI was investigated in a level I trauma center. The primary measure of benefit was the dichotomized GOS 30 d after injury, and primary safety measures were differences in adverse event rates and 30-d mortality. In this study, 100 patients who arrived within 11 h of injury with a Glasgow Coma Scale (GCS) score of 4–12 were enrolled and randomized on a 4:1 basis to receive either intravenous progesterone or placebo; 77 patients received progesterone; 23 received placebo. No serious adverse events were attributed to progesterone. Adverse and serious adverse event rates were similar in both groups, except that patients randomized to progesterone had a lower 30-d mortality rate than controls (RR = 0.43; 95% CI 0.18 to 0.99). Thirty days after injury, the majority of severe TBI survivors in both groups had relatively poor GOS extended and disability

rating-scale scores. Survivors of moderate TBI who received progesterone were more likely to have a moderate-to-good outcome than those randomized to placebo. In addition, results of a recently published randomized controlled trial indicate that progesterone improves the outcome in patients with severe TBI (35). In this study, 159 TBI patients with a GCS \leq 8 were enrolled prospectively within 8 h of trauma. Of these patients, 82 were randomized to receive progesterone, whereas 77 were randomized to the placebo control group. Patients treated with progesterone had lower mortality and more favorable outcomes, as measured by the GOS and the modified Functional Independence Measure Score at 3- and 6-month follow-up (35). These promising data indicate that progesterone may be one of the few pharmacological “golden bullets” for patients with severe TBI. However, this notion warrants further validation in future clinical trials.

NMDA-RECEPTOR ANTAGONISTS

Glutamate is the principal excitatory neurotransmitter in the brain. It acts postsynaptically on three families of ionotropic receptors that are named after their agonists, NMDA, α -amino-3-hydroxy-5-methyl-4-isoxazoleproionic acid, and kainite (36,37). Another receptor class is the metabotropic glutamate receptor (mGluR), which acts via a messenger (G proteins) to modulate biochemical pathways and ion channels. Three subgroups of mGluRs have been characterized, group I (mGluRs1, mGluRs5), group II (mGluRs2, mGluRs3), and group III (mGluRs 4–8). In contrast to ionotropic receptors, mGluRs modulate the release of neurotransmitters (38). mGluRs are activated by prolonged or elevated glutamate release in case of seizures and trauma (39). Glutamate is released from vesicles in presynaptic terminals by a Ca^{++} -dependent mechanism, involving voltage-dependent Ca^{++} channels (36,40). Glutamate may also be released by reverse operation of glutamate transporters, a process that occurs when

Na^{+} and K^{+} gradients are reduced during cerebral ischemia and TBI (41). Glutamate plays a pivotal role in neuronal differentiation, migration, and survival in the developing brain (42).

In TBI it is evident that extracellular glutamate levels are markedly increased, resulting in glutamate-receptor overstimulation. This can lead to secondary adverse events and neuronal cell death (43,44). At the cellular level, prolonged depolarization and subsequent ionic imbalance (that is, increased intracellular calcium levels) can contribute to cerebral edema, which in turn can increase intracranial pressure, leading to vascular compression and possible brain herniation (45). These findings were confirmed by Bullock *et al.* (43) in a clinical study in which sustained elevated intracranial pressure combined with poor patient outcome was significantly associated with increased levels of glutamate in the brain. The knowledge of these pathophysiological circumstances has led to the development of agents that modulate glutamate transmission. The NMDA receptor is the pharmacological target of numerous treatments in a variety of neurological diseases (38). Summarization studies in animal models have provided a large body of evidence that glutamate accumulation in the synaptical fissure is a main cause of cell death. Reduction of glutamate levels or neurotransmission via different pharmacological agents can ameliorate such effects (43,46–48).

A Cochrane analysis identified a total of seven completed, randomized controlled trials in patients with TBI. There were another two randomized clinical trials with three different compounds available for this review.

Selfotel

Selfotel (GCS 19755) is a competitive glutamate antagonist that has been tested in two separate multicenter, double-blind, controlled phase III clinical trials in patients with severe TBI (49). These trials were conducted simultaneously in the United States, Israel, and Europe, with 93 medical centers participating.

Inclusion criteria were a GCS score of 4–8, at least one reactive pupil, and an abnormal computed tomographic scan demonstrating intracranial injury. The protocol required a cerebral perfusion pressure >60 mmHg and intracranial pressure >20 mmHg. The primary endpoint was a demonstration of 10% improvement in the GOS measured 6 months after injury. Patients received 5 mg/kg selfotel or placebo daily for 4 d. Initial treatment was within 8 h of injury. A total of 693 patients were enrolled. Comparison of the two treatment groups showed no difference in mortality rate, with a slight trend in the selfotel group toward worse outcome. The study was prematurely stopped owing to an interim analysis indicating that achievement of improved GOS was highly unlikely. Additionally, data indicated a significant increase of serious adverse effects and high mortality rate in the selfotel treatment group.

Traxoprodil (CP-101.606)

Traxoprodil (CP-101.606) is a substituted 4-phenylpiperidine noncompetitive NMDA antagonist with good brain penetration. Additionally, traxoprodil acts as a postsynaptic NMDA antagonist with a high affinity for receptors containing the NR2B-subunit, which is distributed in forebrain areas vulnerable to injury resulting from trauma or ischemia (50). A phase II clinical study published by Merchant *et al.* (51) investigated pharmacokinetics, safety, and tolerability of traxoprodil in 53 patients (45 patients with mild-to-moderate TBI, 8 with hemorrhagic stroke). Outcome measures included a battery of neurobehavioral tests. Although there were no adverse effects reported, there were no statistical differences in outcome. A more recent, double-blind, placebo-controlled phase III trial (52) included 444 patients who received taxoprodil or placebo infusion within 8 h of severe TBI. Outcome measures were function at 6 months after TBI. Although this study yielded intriguing results, it did not lead to definitive recommendations for treatment.

D-CCP-ene (EAA 494)

D-CCP-ene (EAA 494) is a competitive NMDA agonist that has been tested in a double-blind, placebo-controlled, phase III trial. Results of this trial have not been published but were discussed in Narayan *et al.* (53). A total of 920 patients were recruited in 51 European treatment centers. Patients received either D-CCP-ene twice a day for a period of 5 d or placebo. The primary endpoint was the GOS score 6 months after TBI. Patients in the treatment group had a slightly, non-statistically significant, worse outcome than patients in the placebo group. Therefore, D-CCP-ene is not recommended in the treatment of TBI.

Magnesium Sulfate (MgSO₄)

Magnesium is an intracellular cation that is known to modulate NMDA-receptor permeability to calcium and sodium. Furthermore, magnesium is a potent calcium-channel blocker that modulates intracellular calcium activity by a noncompetitive NMDA-receptor channel block (54). Low levels of magnesium can generate an impairment of the ATPase pump function (55), leading to a reduction of intracellular ATP and thus increasing the intracellular calcium levels. Head-injured patients are at high risk of developing hypomagnesaemia, which can persist for several days (56,57). Animal head-injury models have demonstrated that this reduction in magnesium levels is associated with poor neurological outcome and increased mortality (58). Restoring these levels reduces brain edema and improves neurological and cognitive outcomes. Magnesium has been shown to be neuroprotective in experimental TBI in rodent models (59–61). This potential for improved outcome led to randomized, controlled clinical trials. Arrango *et al.* recently published a systematic review identifying two studies with 75 randomized patients (62). GOS results at 6 months indicated that there is no role for MgSO₄ in the treatment of TBI. A subsequent double-blind, monocentric, clinical phase II trial that included 499 patients with mild to severe TBI (GCS total 3–12)

(63) confirmed no improvement in outcome with administration of magnesium in TBI. Primary outcome parameters were survival, seizure occurrence, and neurobehavioral functioning 6 months after TBI. The initial serum level target of magnesium was 1.25–2.4 mmol/L, but owing to concerning trends in deaths and blood pressure the study was restarted with a lower target concentration of 1.0–1.85 mmol/L. A loading dose of magnesium was administered within the first 8 h of injury. There was higher mortality in the higher magnesium dose group than with the placebo. These studies suggested that magnesium may not be neuroprotective and in fact may be harmful.

In summary, excessive activation, followed within a relatively short time by desensitization and loss of functional NMDA receptors, may explain the pre-clinical and clinical experience with NMDA-receptor antagonists, as well as suggest alternative modes of treatment. This hypothesis was tested in a mouse model of closed head injury and the result not only confirmed the hypothesis, showing approximately 50% lower levels of NMDA receptor at 7 d after injury, but also demonstrated that the activation of these receptors (not inhibition) at 24 h after injury led to remarkably improved function (64,65).

SYNTHETIC CANNABINOIDS

In the last decade the endocannabinoid system has been examined for its potential neuroprotective role. This system consists of two receptors, CB1 and CB2, and three types of endocannabinoid ligands. All known types of endogenous cannabinoids are derivatives of arachidonic acid. The CB1 receptor is present mainly in the central nervous system (CNS) and in numerous peripheral tissues, whereas CB2 is found mostly in organs of the immune system but not in the brain (66–69). Arachidonylethanolamide (anandamide) was the first endocannabinoid to be identified (70), followed by 2-arachidonoyl glycerol (71). A third endocannabinoid, 2-arachidonoyl glyceryl ether (noladin ether), was reported in 2001 (72). Unlike

the classic neurotransmitters, such as dopamine, serotonin, and norepinephrine, the endocannabinoid anandamide is present in very low concentrations in the brain and is formed on demand from a precursor, N-arachidonoylphosphatidylethanolamine (73). In most of their pharmacological activities, these body constituents parallel the effects of Δ^9 tetrahydrocannabinol, the active constituent of marijuana, but the effect of endocannabinoids is shorter in duration because of their quick cellular uptake and hydrolysis by fatty acid amide hydrolase (74).

The neuroprotective effects of cannabinoids include inhibition of the release of glutamate and inflammatory cytokines. Cannabinoids also counteract the vasoconstrictive effect of endothelin-1. These effects have been demonstrated in cell culture and animal models and extensively described in reviews (75,76).

A synthetic, nonpsychotropic cannabinoid is HU-211 (dexanabinol). This compound was found to exhibit pharmacological properties characteristic of a noncompetitive NMDA-receptor antagonist (77,78). HU-211 also blocks tumor-necrosis factor synthesis and has antioxidant properties, inhibiting release of ROS (79–81). Because glutamate, ROS, and tumor-necrosis factor are well known to be involved in the pathophysiology of brain injury (82,83), the above observations led to clinical trials. Phase I and II trials demonstrated (84,85) that HU-211 significantly improves the neurological outcome of head-injured patients. Results of a multicenter, placebo-controlled, phase III clinical trial have been published recently (86). In this study, patients were randomized to receive a single dose of intravenous HU-211 (dexanabinol) (150 mg) or placebo. A total of 846 patients were prospectively enrolled and randomized into the HU-211 and placebo-control treatment groups. Of the entire patient population, an equal number of patients showed an unfavorable outcome at 6 months, as determined by the extended GOS as the primary outcome parameter in this study (86). The promising results from previous phase I and II clinical trials

could not be replicated. There was no difference in outcome after 6 months in the HU-211 treatment group (odds ratio 1.04; 95% CI 0.79 to 1.36). Improvement in intracranial pressure control was not recorded, and subgroup analysis showed no benefits of HU-211 treatment.

MONOAMINERGIC SUBSTANCES

Monoaminergic substances are thought to modulate functional recovery after established brain injury. The etiology is multifactorial (87). Previous studies have focused on prevention of secondary injury, whereas the focus of this substance is on repair once secondary injury has occurred. In animal models after experimental head injury, levels of norepinephrine, dopamine, and epinephrine are markedly increased. Additionally, administration of amphetamine after TBI in a rat model showed improved neurological outcome (88).

Methylphenidate (Ritalin) is a dopamine reuptake inhibitor that has been tested in the treatment of neurobehavioral disorders following TBI (89). The exact mechanism of action is not yet fully understood, but methylphenidate seems to act by altering the reuptake and consequently the efficacy of different aminergic CNS neurotransmitters. The presumed mechanism is interference with dopamine reuptake. The potency of blocking the norepinephrine transporter is lower (90). Methylphenidate has proven clinical safety and has been safely administered to patients following TBI (91,92). Preliminary results show that patients have improved recovery and cognitive skills after TBI. A recent published Cochrane Database Review mentioned that there is insufficient evidence to support the administration of methylphenidate or other related agents (for example, amantadine) in TBI. None of the cited references met the inclusion criteria (87). One study (93) investigated the effect of methylphenidate on hospital and intensive care unit (ICU) length of stay in patients with TBI. In this prospective, randomized, double-blind clinical study 40 patients with severe (GCS 5–8) and 40 patients with mild TBI

(GCS 9–12) were treated with 0.3 mg/kg methylphenidate per dose by the second day after TBI and were treated until discharge. Methylphenidate was associated with reductions in ICU and hospital length of stay by 23% in severe TBI patients ($P = 0.06$ for ICU and $P = 0.029$ for hospital stay). In the moderate TBI group only the ICU duration was significantly shorter ($P = 0.05$). Currently a phase III clinical trial is being conducted to evaluate the effects of methylphenidate in the setting of TBI in children.

CYCLOSPORINE

Cyclosporine A (CsA) may be a potential neuroprotective treatment following acute TBI. In animal models it has been shown that administration of CsA following acute, severe TBI reduces the amount of damaged tissue when given following the event (94–97). The exact mechanism of action responsible for neuroprotection remains unclear. CsA inhibits mitochondrial dysfunction in the CNS, preventing calcium efflux. By interfering with calcium release from mitochondria, the secondary cascade of events leading to persistent damage within the CNS is presumed to be interrupted (98–100). Defining the optimal dosing to achieve therapeutic concentrations in the brain with minimal systemic consequences is important. CsA is metabolized by the hepatic cytochrome P-450 3A enzyme into more than 18 metabolites (101). Results of a phase II clinical trial (102) have been published recently. In this prospective, randomized, placebo-controlled clinical trial a dose escalation was performed to obtain data regarding CsA effects in TBI patients as well as to identify optimal dosage in 30 patients with severe TBI (GCS 4–8). It was shown that patients with severe TBI demonstrate a rapid clearance and larger distribution volume of CsA. This effect will need to be accounted for in future safety and efficacy studies.

CALCIUM-CHANNEL BLOCKERS

Calcium-channel blockers reduce the influx of calcium into the cell by blocking

the calcium channels. In the setting of experimental TBI, a rapid increase of extracellular calcium is observed based on increased Ca^{2+} permeability and mitochondrial Ca^{2+} release. There is still uncertainty about the consequences, but it is suggested that ROS are created, inducing cellular damage and death (103–105). Calcium-channel blocker use has been suggested for prevention or treatment of cerebral vasospasm after acute traumatic brain injury. The known side effects of the drugs (induced hypotension, cerebral vasodilatation, and impaired cerebrovascular reactivity) call into question the utility of calcium-channel blockers in TBI. Nimodipine is known for prevention of vasospasm in aneurysmal subarachnoid hemorrhage and has been shown to have neuroprotective properties (103). In the early 1990s, HIT (Head Injury Trial) I and II (106–110) performed in unselected TBI patients in Europe indicated a 4% absolute improvement and 8% relative improvement for favorable outcome in nimodipine-treated patients. These results were not statistically significant. A systematic Cochrane Database Review included all six existing clinical trials (111). These were RCTs with a total of 1862 participants. Risk of death was reported in five trials, and the pooled odds ratio (OR) of these trials was 0.91 (95% CI 0.70 to 1.16). For the six trials reporting death and severe disability (unfavorable outcome), the pooled OR was 0.97 (95% CI 0.81 to 1.18). For two RCTs reporting the risk of death in a subgroup of traumatic subarachnoid hemorrhage patients, the pooled OR was 0.59 (95% CI 0.37 to 0.94). Thus, the role for calcium channel blocker in acute TBI remains unclear. A beneficial effect of nimodipine in a subgroup of brain injury patients with subarachnoid hemorrhage was shown but further clinical phase III studies are needed to ascertain beneficial effects in TBI versus the known risks.

MODULATORS OF THE KININ/KALLIKREIN SYSTEM

Activation of the kallikrein-kinin system occurs after trauma (112). Kinins are

thought to be involved in the inflammatory response. Bradykinin is a potent stimulator of nitric oxide formation, cytokines, free radicals, and excitatory amino acids as well as a stimulator of increased intracellular Ca^{2+} (113,114), which can lead to blood-brain-barrier dysfunction (113,115). Two G-protein (B1 and B2)-coupled receptors are known to mediate the effects of kinins. Bradykinin acts via the B2-receptor (116). Bradykinin receptor antagonists given after experimental TBI resulted in improved neurological outcome in animal models (117,118).

Bradycor (CP-0127)

Bradycor (Delbitant), a peptide compound B2-receptor antagonist, was tested in a pilot, single-blind clinical study in 20 patients (119). Results showed reduction of intracranial pressure and significant prevention in deterioration of GCS. In a multicenter randomized, placebo-controlled trial (120) with 139 patients, bradycor-treated patients showed improvement in GOS measured 3 months after trauma. Results appeared promising, indicating a positive trend in intracranial pressure, neuropsychological tests, GOS score, and death rate, although none of the results were statistically significant compared to the placebo-treated group. A larger randomized study is needed to confirm and define this promising result.

Anatibant (LF16-0687Ma)

Anatibant, a nonpeptide B2-receptor antagonist, has been shown to be effective at minimal concentrations (121) and has been tested in animal models. Potential benefits include decreases in brain edema, improved neurological function recovery, and decreased inflammatory response (117,118,122). A phase I clinical trial in healthy volunteers showed no safety issues (unpublished data). Recently anatibant was investigated in a phase I clinical study (123) in patients with severe TBI. In this multicenter, double-blind, randomized, placebo-controlled trial, patients with TBI and GCS <8 received anatibant

(3.75 or 22.5 mg) subcutaneously within 8–12 hours after TBI. The objective was to test the pharmacokinetics of anatibant in the setting of severe TBI. GOS at 3 and 6 months indicated a positive trend toward the higher concentration, but small sample size (anatibant $n = 10$ per group, placebo $n = 5$) are limiting factors for interpretation of the results.

CONCLUSION

The golden bullet in the treatment of acute TBI has not yet been determined. Unfortunately, most of the promising therapeutic strategies derived from experimental animal studies have failed in translation to the clinical setting of TBI. The rationale for this disappointing failure is likely multifactorial. Pharmacological compounds that are currently in clinical use may be missing their target, both from a morphological perspective by not reaching an adequate concentration within the intracranial compartment, and from a kinetic point of view, by missing the appropriate timing for the therapeutic window of opportunity.

Future therapeutic protocols should be designed to allow for prehospital care personnel to administer specific pharmacological agents at the accident site. In addition, there is an ongoing need for continuing high-quality basic research studies in search of new therapeutic compounds. The unexpected failure of the CRASH trial in 2004, which revealed that complete inhibition of posttraumatic neuroinflammation by administration of high-dose methylprednisolone leads to a significantly increased mortality after TBI (11,12), indicates that future anti-inflammatory strategies will have to be more subtle and sophisticated. Promising new findings have been made in molecular mechanisms of TBI, and many experimental substances await testing in the clinical setting. For example, peroxisome proliferator-activated receptors have recently emerged as potent antiinflammatory transcription factors that when used alone or in combination with endocannabinoids may prove to be pivotal antiinflammatory and neuroprotective

agents in the setting of TBI (124,125). In addition, selective targeting of the innate immune response after trauma, such as by pharmacological inhibition of the complement cascade at various levels of its activation pathways, has recently emerged as a new promising therapeutic strategy in experimental TBI models (126–129). Exciting treatment possibilities such as these promise a riveting future for research in the treatment of TBI.

DISCLOSURE

The authors declare that they have no competing financial or proprietary interests with regard to this publication. Particularly, none of the authors have any financial relationships, interests, or shares related to any of the therapeutic agents discussed in this manuscript.

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