CP-101,606:
An NR2B-Selective NMDA Receptor Antagonist

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INTRODUCTION

Glutamate and aspartate play dual roles in the central nervous system as essential amino acids and the principal excitatory neurotransmitters. The theory of excitotoxicity presents the paradoxical view that these excitatory amino acids may also become endogenous neurotoxins any time the brain’s energy homeostasis is compromised (16,23,42,59). Cerebral ischemia and traumatic brain injury result in acute energy depletion and cellular depolarization. This triggers a dramatic increase in extracellular glutamate levels (10,11) due to presynaptic glutamate release and/or reversal of neuronal and glial glutamate transporters (63,64). The result is a prolonged overactivation of glutamate receptors which, through an incompletely understood cascade of events, leads to neuron death. Glutamate receptor activity is also hypothesized to play a role in the neuron death associated with chronic neurodegenerative conditions such as Alzheimer’s disease and Parkinson’s disease. In these latter conditions, subtle but chronic deregulation in neuronal energy metabolism renders neurons susceptible to excitotoxicity from physiological glutamate receptor activity (1,23,36). Given the premise of excitotoxicity as a central event in neuron loss associated with both acute and chronic neurodegenerative conditions, glutamate-receptor inhibition has been an aggressively pursued therapeutic strategy to treat these conditions.

There are four major classes of glutamate receptors: N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), kainate, and metabotropic (2). Of these, NMDA receptors appears to be especially important to the excitotoxic process. The NMDA receptor is an ion channel gated by synaptically released glutamate in the presence of the coagonist glycine (29,32) and concomitant depolarization (38). The NMDA receptor is permeable to Na⁺ and Ca²⁺; it is Ca²⁺ influx through the receptor that
appears to play the critical role in neurotoxicity (14,37). Neurons in primary culture are exquisitely sensitive to the toxic effects of NMDA-receptor activation, and NMDA-receptor antagonists protect cultured neurons from both NMDA and glutamate toxicity (16,57). More significantly, NMDA-receptor antagonists reduce neuron loss in vivo in animal models of focal ischemia (39) and head trauma (7).

The neuroprotective effect of NMDA-receptor antagonists in experimental systems prompted considerable interest in the therapeutic potential of this class and stimulated research into the pharmacology of NMDA receptors. NMDA-receptor activity may be attenuated by blockade of the glutamate binding site, the glycine-co-agonist binding site, and the receptor-associated ion channel. Several prototype antagonists for these various sites have progressed into clinical trials, especially for stroke and head trauma (50).

Side effects at therapeutic drug levels have been a significant problem, however, which has hindered the development process (50). In particular, both glutamate-competitive antagonists and channel-blocking agents cause cardiovascular effects and psychotic symptoms in humans. Although the physiological basis for these side effects is not yet understood, in rodents these types of compounds also cause locomotor hyperactivity and a paradoxical neuronal hyperexcitability manifested as neuronal vacuolization in cingulate and retrosplenial cortices (55).

Antagonists at the glycine-coagonist site cause less locomotor activation and do not cause neuronal vacuolization at neuroprotective doses in rodents, suggesting that this class of antagonists may be better tolerated in humans (30). Unfortunately, physicochemical problems associated with the quinoxalinedione nucleus (solubility, brain penetration, protein binding) have hindered efforts to bring this class forward in the clinic (59) and only one compound, GlaxoWellcome’s GV-150526, has progressed to advanced stages of development. Thus, new NMDA-receptor antagonists are sought to test the therapeutic potential of NMDA-receptor inhibition.

CP-101,606 represents a fourth mechanistic class of NMDA-receptor antagonist. This class is unique in that it is specific for a subtype of NMDA receptors which contain the NR2B subunit and are expressed in the forebrain. Below are reviewed the synthesis and pharmacology of CP-101,606, including its profile of activity in experimental models of neurodegeneration. This is followed by a summary of the clinical experience with the compound to date.

CHEMISTRY

CP-101,606, C_{20}H_{25}NO_{3}, has the chemical name (1S,2S)-1-(4-hydroxyphenyl)-2-(4-hydroxy-4-phenylpiperidino)-1-propanol and its structure is illustrated in Fig. 1 (13). The compound is a white powder which has a melting point of 203 to 204°C and [α]D of +56.9° (c = 0.26, methanol). As a free base, the compound has low aqueous solubility, however, it readily forms acid-addition salts which greatly improve water solubility. In particular, the mesylate salt crystallizes as a stable trihydrate with good water solubility (> 10 mg/ml).

Commencing with commercial 4-hydroxypropiophenone, CP-101,606 is readily prepared in a linear, eight-step synthesis (Fig. 2). Recrystallization of the D-(−)-tartaric acid addition salt effects the resolution.
SELECTIVITY FOR NR2B SUBUNIT-CONTAINING NMDA RECEPTORS AND IN VITRO PHARMACOLOGY

The NMDA receptor is composed of multiple protein subunits (48). Five subunits have been cloned to date, NR1 and NR2A-D. Expression studies indicate the functional receptor is composed of at least one NR1 subunit and one or more of the NR2 subunits (5,12,34,35,47,62). In the adult mammalian brain, the NR1 and NR2A subunits are widely expressed. In contrast, NR2B subunit expression is restricted to forebrain regions, including cortex, hippocampus, and striatum, whereas the NR2C subunit is expressed in cerebellum and the NR2D subunit is restricted to midbrain. The agonist-binding site and channel-blocking NMDA-receptor antagonists discovered to date display little selectivity for different receptor subunit combinations. The first compound identified to display significant subtype selectivity was ifenprodil. Williams (69) demonstrated that ifenprodil was both more potent and efficacious for blockade of ion current through NR1/NR2B receptors than for NR1/NR2A receptors; subsequent studies indicated a similar selectivity for NR2B over NR2C- and NR2D-containing receptors (68).

CP-101,606 arose from studies of structure/activity relationships of ifenprodil analogs aimed at increasing potency for NMDA receptors and selectivity for NMDA over \(\alpha_1\)-adrenergic receptors (13). These studies were initiated before the existence of different NMDA-receptor subtypes was fully appreciated. The primary assay used was inhibition of glutamate-induced death in rat hippocampal cultures. As potency increased in this assay, evidence of selectivity emerged as the compounds failed to similarly inhibit glutamate toxicity in cerebellar granule neuron cultures. CP-101,606 was identified as a lead compound (EC\(_{50}\) = 11 nM for inhibition of glutamate toxicity in hippocampal cultures) (13,42) and the racemate was radiolabeled. The distribution of the racemic \(^3\text{H}\)CP-101,606 binding site in autoradiographic studies of rat brain also indicated a high degree of selectivity for forebrain neurons (Fig. 3). At the time these studies were being completed, Seeburg’s group reported the molecular cloning of the NR2A-C NMDA-receptor subunits and their differential expression pattern in rat brain (47). We recognized that the distribution of the racemic \(^3\text{H}\)CP-101,606 binding sites overlapped completely with the
forebrain distribution of the NR2B subunit and hypothesized that CP-101,606 was selective for NR2B-containing receptors. NR2B subunit selectivity also accounted for the selectivity in the neurotoxicity assays, since the forebrain hippocampal neurons expressed the NR2B subunit whereas the cerebellar neurons expressed the NR2C subunit. NR2B selectivity was subsequently confirmed in experiments with *Xenopus oocytes* (D. D. Mott, S. Zhang, M. S. Washburn, M. Fendley, R. Dingedine, W. Volberg, and S. B. Sands, un-
published observations) and Chinese hamster ovary cells (5) transfected with various NMDA-receptor subunit combinations: CP-101,606 blocked NMDA-induced currents in receptors formed from NR1 and NR2B subunits but had little effect on receptors formed from NR1 and NR2A or NR2C subunits.

Receptor-binding studies, including those with racemic [3H]CP-101,606, elucidated the pharmacology of CP-101,606 (42). CP-101,606 does not interact directly with the glutamate or glycine binding sites or with the channel pore site labeled with [3H]TCP. Instead, inhibition of NMDA receptors results from interaction with an allosteric modulatory site labeled by racemic [3H]CP-101,606. This binding site appears to be closely related to that for the polyamines, since spermine and spermidine, but not putrescine, displace racemic [3H]CP-101,606 binding with activity similar to that for potentiation of [3H]TCP binding to the NMDA-receptor channel. The binding site is also apparently overlaps with that for ifenprodil. Affinity for the racemic [3H]CP-101,606 binding site of CP-101,606 (k_d = 10 ± 1 nM) and a range of analogs correlates closely with EC_{50}s for inhibition of glutamate toxicity in hippocampal neurons. This indicates that the neuroprotective effect of the compound is mediated through interaction with the binding site.

At the level of the single NMDA-receptor channel, CP-101,606 decreases both the open dwell time and the frequency of channel opening (5). The molecular mechanism through which CP-101,606 causes these changes in receptor activity is being actively investigated. Brimecombe et al. (6) have found that glutamate at position 201 (E201) of the N-terminal extracellular domain of the NR2B subunit is essential for the inhibitory effect of CP-101,606. Substitution at this site also diminishes the inhibitory effects of haloperidol but not ifenprodil, two other NR2B-selective NMDA antagonists. Interestingly, E201 appears to be critical for the stimulation of NMDA-receptor activity by polyamines (19). This overlap between the CP-101,606 and polyamine binding sites at the molecular level is consistent with data from radioligand binding studies discussed above which suggested such an overlap (42). Evidence is accumulating that the polyamines regulate NMDA-receptor activity by modulating the proton sensor of the receptor (66); Dingledine and co-workers (19,49) have hypothesized that both CP-101,606 and ifenprodil inhibit NMDA-receptor activity by potentiating proton inhibition. These ongoing studies will undoubtedly provide further information on the mechanism of action of CP-101,606 and also give insight into the physiological regulation of NMDA receptor activity.

**IN VIVO STUDIES**

Initial studies in rats indicated that CP-101,606 readily crossed the blood brain barrier to inhibit forebrain NMDA receptors (56). Unlike channel-blocking and glutamate binding site-competitive NMDA-receptor antagonists (60), CP-101,606 did not cause locomotor hyperactivity even at very high doses (Fig. 4) or produce vacuolization in cingulate/retrospenial cortex (56). Based on the pharmacological profile *in vitro* and these preliminary results, the compound was tested for efficacy in a number of animal models of traumatic brain injury and ischemia to assess the potential for therapeutic effects in neurodegenerative conditions in humans. The results of these studies are summarized below.
Acute traumatic brain injury results in a complex cascade of events ultimately leading to neuron loss both, at and distal to, the site of injury (40). Mechanical insult can result in direct neuron damage or mechanical damage secondary to formation of space-filling lesions such as hematomas. Secondary changes in brain metabolism, intracranial pressure, and tissue perfusion can lead to edema and ischemia, which may exacerbate focal mechanical damage and induce a more widespread secondary neuron loss. NMDA-receptor activation has been hypothesized to play a critical role in this pathological cascade. Traumatic brain injury results in a prolonged increase in extracellular glutamate (10), which may cause overactivation of NMDA receptors. This, in turn, may directly cause neuron...
death and/or hypermetabolism and cell swelling, which contribute to pathological edema and increased intracranial pressure. NMDA-receptor activation may also provoke cortical spreading depression (see below) which can contribute to neuron loss at sites distal to the focal insult. We have found that CP-101,606 reduces a number of these pathological processes in experimental models of traumatic brain injury.

The effects of CP-101,606 were evaluated on brain edema and deterioration in memory function and neurological score after lateral fluid percussion brain injury in rats (53,54). Fifteen minutes after a moderate fluid percussion injury (2.5 atm), animals received CP-101,606 (or CP-98,113, which is racemic CP-101,606) as a 5 mg/kg intraperitoneal bolus followed by a continuous subcutaneous infusion of 1.5 mg/kg/h of drug for 24 h. This administration paradigm produced a constant plasma concentration of about 200 ng/ml throughout the treatment period. Animals were allowed to recover for 42 h after treatment and were then tested for memory retention in a previously learned Morris water maze task. CP-101,606-treated animals showed significantly less impairment than vehicle-treated animals as indexed by decreased time to locate the submerged platform and more swim time spent in the vicinity of the platform. CP-101,606 treatment also significantly reduced edema as measured by the wet weight-dry weight technique (53) in cortical tissue dissected from the region surrounding the impact site. In a separate study in
rats, neurologic status, scored as a series of strength, balance, and locomotor functions, were evaluated 1 and 14 d after injury. Animals treated with racemic CP-101,606, by the same dosing regimen described above, had significantly less neurological impairment at each time point.

The effect of CP-101,606 on the increase in intracranial pressure which occurs after a closed head injury in rat was also examined (H. Goldman, unpublished observations). In this model (20), a weighted pendulum is released to impact the premaxillary and maxillary bones of the skull with a force of 60 to 85 pounds. This produces a moderate concussion without skull fracture or brain contusion which results in a prolonged increase in intracranial pressure, attributable to injury-induced edema. In untreated animals, intracranial pressure increased in two phases: an initial 2.5-fold increase in the 4 h immediately after injury, followed by a slower rise over the next 20 h to a maximum about 4-fold above normal (Fig. 5). Animals received CP-101,606 as a 5 mg/kg i.p. bolus followed by a continuous subcutaneous infusion of 1.5 mg/kg/h (targeting a sustained plasma level of 200 ng/ml) beginning 15 min after injury. CP-101,606 reduced by approximately 50% the initial rise in intracranial pressure and completely eliminated the slower increase at the later time (Fig. 5).

CP-101,606 was also evaluated for neuroprotective activity in a rat model of acute subdural hematoma. Subdural hematoma is a common complication in severe head trauma and results in mechanical damage and ischemia (9). In this model (46), subdural hematoma was produced by slow injection of 0.4 ml of autologous blood into the parietal subdural space. The drug was administered at two doses (low dose: 2 mg/kg bolus intraperitoneal injection followed by continuous subcutaneous infusion of 1.5 mg/kg/h; high dose: 5 mg/kg bolus and continuous infusion of 1.5 mg/kg/h) starting 30 min after induction of a hematoma. Animals were sacrificed 4 h after injury and infarct volume was determined in serial coronal brain sections stained with hematoxylin and eosin or cresyl violet. CP-101,606 reduced infarct volumes by 29 and 37% at the low and high doses, respectively (67). The reduction in lesion size at the high dose (estimated sustained CP-101,606 plasma level of 200 ng/ml) was comparable to the neuroprotective effects observed with other NMDA antagonists studied in the same laboratory.

Finally, CP-101,606 was examined on induction of the immediate early gene \(c-fos\) caused by a stab wound injury in anesthetized rat. Focal CNS injury or ischemia results in a robust induction of \(c-fos\) expression throughout the injured hemisphere (4,28); \(c-fos\) induction is inhibited by NMDA-receptor antagonists (4,17,27,28,31) and it has been hypothesized that this response may be a component of the intracellular signaling cascade activated by NMDA receptors that results in neuron death (21,24,45,61). Thus, the effect of CP-101,606 on \(c-fos\) induction as a marker of CNS injury was examined to further investigate the neuroprotective potential of the compound. A unilateral stab wound to the parietal cortex of rat caused an increase in \(c-fos\) mRNA in the injured cortical hemisphere which was evident within 30 min of injury, peaked at 1 h at 2.5-fold above that in an uninjured control group, and returned to basal level at 4 h (43). CP-101,606, administered intravenously 30 min before injury, inhibited \(c-fos\) mRNA induction in a dose-dependent fashion, with an \(ED_{50}\) of 4.1 mg/kg. The average plasma level of CP-101,606 at the \(ED_{50}\) dose was estimated to be 189 ng/ml.

The results outlined above indicate that CP-101,606 significantly reduces functional deficits caused by traumatic brain injury in several rodent models. These include reduced
behavioral and neurological deficits, reduced increases in intracranial pressure, and reduced infarction and c-fos mRNA induction. Again, efficacy of CP-101,606 in these models is associated with plasma levels of approximately 200 ng/ml. The level of efficacy with the compound is comparable to that obtained with other classes of NMDA receptor antagonists.

Cerebral Ischemia

As discussed above, cerebral ischemia may contribute to the neuron loss after traumatic brain injury. However, the most common cause of cerebral ischemia-related brain damage is stroke. While the etiology and affected brain regions vary across patients, stroke often involves occlusion of the middle cerebral artery (MCA-o) and experimental models of stroke have focused on MCA-o. Notwithstanding, these models are almost as diverse as

Fig. 5. The effect of CP-101,606 on the rise in intracranial pressure (ICP) caused by moderate concussive force in rat. Prior to trauma, ICP was 4.2 ± 0.2 mm Hg. In vehicle-treated animals, there was a 50% increase in ICP within 30 min following impact. This increase continued to 1 h post-trauma, when it stabilized at a level approximately 2.5 times greater than normal. This first phase of increased ICP was followed by a second phase that can be seen 6 h post-trauma. By 24 h post-trauma, ICP was almost 4 times that seen prior to the trauma. When CP-101,606 administration was initiated 15 min after the concussive impact, it significantly decreased the rise in ICP measured from 1 to 24 h post-trauma (*, p < 0.05).
the human disease, with important variables including species, location, and duration and means of occlusion. Given the clear face validity, MCA-o models have been used to validate entry of a compound into clinical trials for stroke and to set target therapeutic drug levels and/or treatment procedure. However, the predictive power is far from established, with a number of the compounds showing activity in animal MCA-o models having failed to demonstrate efficacy in clinical stroke trials (25). This indicates that there is much to be learned about the pathophysiology of ischemia-induced neuron loss and encourages further testing of novel compounds in both the animal models and in the clinic.

To date, the effects of CP-101,606 have been evaluated in models of permanent MCA-o in cat and rat. In the cat (18), CP-101,606 was administered 15 min prior to MCA-o as an intravenous bolus of 1 mg/kg followed by continuous intravenous infusion of 7.5 μg/min/kg. This dosing regimen was designed to deliver sustained plasma drug levels of 200 ng/ml for the 5-h post-occlusion survival period. Infarct volume was evaluated by diffusion-weighted magnetic resonance imaging (MRI) at 1 and 5 h following MCA-o and by staining of coronal sections taken after sacrifice with the vital dye, triphenyl tetrazolium chloride. In addition, lactate levels in the territory of the middle cerebral artery were determined by microdialysis. CP-101,606 reduced infarct volume by 62.9% as measured by vital dye staining (Fig. 6). A similar reduction in infarct volume was measured by MRI. Lactate levels in untreated animals increased by approximately 300% in the area of the middle cerebral artery by 1 h after occlusion and remained elevated for the duration of survival. In contrast, lactate levels rose only slightly in animals treated with CP-101,606. These effects of CP-101,606 place it among the most effective agents tested in this paradigm (18).

The effect of CP-101,606 was also examined in two studies of permanent MCA-o in rats. Dosing paradigms were again designed to maintain plasma levels of CP-101,606 at 200 ng/ml for the 24-h post-occlusion survival interval (5 mg/kg bolus intraperitoneal injection followed by continuous subcutaneous infusion of 1.5 mg/kg/h). In one study the middle cerebral artery was electrocoagulated from the lenticulostriate artery to the point crossing the inferior cerebral vein in male Fischer 344 rats. CP-101,606 significantly improved neurological scores (rated according to Bederson et al., ref. 3) 24 h after infarction (mean ± S.E.M.: CP-101,606 = 1.85 ± 0.9; control = 2.12 ± 0.9; two-tailed t-test, p = 0.04). However, there was no effect on infarct size (mean ± S.E.M.: total infarct size in mm²: CP-101,606 = 111.8 ± 5.4; control = 119.4 ± 7.5). In a second study, the middle cerebral artery was occluded by the suture method (33,63) in male Sprague-Dawley rats. At the time of sacrifice (24 h after MCA-o), 90% of the animals treated with CP-101,606, and 40% in the vehicle-treated group survived. Despite this significant improvement in survival, there was no effect of the compound on infarct size.

In summary, CP-101,606 significantly reduces the pathological sequelae of cerebral ischemia caused by occlusion of the middle cerebral artery in animal models. This includes reduction in infarct volume and lactate accumulation in cat and reduction in neurological deficits and mortality in rats. As for the traumatic brain injury models, efficacy of CP-101,606 in the ischemia models is associated with plasma levels of approximately 200 ng/ml. The lack of effect of the compound on infarct size in the rat is puzzling, given the improvement in functional outcome in this species and the efficacy in the cat MCA-o and in the rat subdural hematoma models. It is possible that a species effect accounts for the difference in results in cats and rats in the MCA-o models, since both the cerebral ar-
Fig. 6. The effect of CP-101,606 on infarct size after permanent middle cerebral artery (MCA)-occlusion in cats. Cats were subjected to unilateral, permanent occlusion of the MCA during continuous infusion of CP-101,606 or vehicle. Frozen coronal sections of cat brains were immersion fixed in triphenyl tetrazolium chloride (TTC). The area of ischemic damage was visualized as the zone of pallor in the region of cortex and striatum and was quantified by image analysis by a blinded observer. A) Section from an animal treated with vehicle. B) Section from an animal treated with CP-101,606. CP-101,606 reduced total infarct volume by 62.9%. Reprinted from ref. 18 with permission from Waverly Press.
Architecture and circulation differ significantly between these two species. The difference in infarct size reduction observed in the subdural hematoma vs. MCA-o models in rat may relate to differences in both the location and duration of the ischemia in these two types of models. Nonetheless, these results highlight the fact that much remains to be learned about the pathological consequences of cerebral ischemia and the role of NMDA-receptor activity in these processes. It will be important to further evaluate CP-101,606 in additional models of cerebral ischemia, such as models of transient MCA-o.

Cortical Spreading Depression

In order to further evaluate the neuroprotective potential of CP-101,606, we investigated the effect of the compound on cortical spreading depression, a process that may be integral to the cascade leading from CNS injury to neuron death. Cortical spreading depression is a propagating wave of cellular depolarization that can be induced by localized trauma or ischemia and spreads from the area of insult across the cortical surface. NMDA-receptor activation appears to be essential for the initiation and propagation of cortical spreading depression since cortical spreading depression is blocked by competitive and non-competitive NMDA-receptor antagonists (51,52). It has been hypothesized that cortical spreading depression emanating from the site of injury causes secondary damage in the penumbra by disrupting ion homeostasis and producing lethal energy demands on neurons already in a compromised state (17,26). In the model used (43), cortical spreading depression was induced in rats by electrical stimulation of the parietal cortex. CP-101,606 administered by intravenous infusion caused a dose-dependent decrease in rate of cortical spreading depression propagation and a reduction in the amplitude of depolarization. Cortical spreading depression was completely inhibited at 60 min after administration of CP-101,606 as a 2.25 mg/kg intravenous bolus, followed by a 2.25 mg/kg/h intravenous infusion. This dosing regimen resulted in sustained CP-101,606 plasma levels of 250 ng/ml. These plasma levels are similar to those associated with efficacy in trauma and ischemia models described above.

Summary of In Vivo Studies

CP-101,606 improves functional outcome in a variety of animal models of traumatic brain injury and cerebral ischemia. The compound reduces infarction caused by cerebral ischemia in two of three models. CP-101,606 also completely inhibits injury-induced increase in c-fos mRNA and cortical spreading depression, two putative components of the cascade leading from CNS injury to NMDA-receptor activation to neuron death. Given the selectivity of the compound for the NR2B subunit, these results suggest that this subtype of NMDA receptor is fundamentally involved in this cascade. Thus, inhibition of this receptor subtype may provide neuroprotective efficacy in neurodegenerative conditions in humans. The efficacy of CP-101,606 in these models is achieved at plasma concentrations of ~200 ng/ml. CP-101,606 does not, however, cause locomotor hyperactivity or neuronal vacuolization even at considerably higher plasma concentrations. The lack of effects of the compound on these latter measures suggests that neuroprotective efficacy
may be achievable with relatively fewer of the side effects that have plagued development of other NMDA-receptor antagonists. This putative favorable efficacy/side effect ratio is hypothesized to derive from the NMDA receptor-subtype selectivity of the compound. These positive results in animal models prompted initiation of clinical trials of CP-101,606 for the treatment of traumatic brain injury.

**CLINICAL EXPERIENCE**

To date, the effects of CP-101,606 after intravenous infusion has been studied in approximately 60 healthy volunteer subjects. Both the rate and duration (up to 72 h) of infusion have been varied. The maximum tolerated mean plasma concentration of CP-101,606 was 4200 ng/ml, approximately 20-fold higher than the putative therapeutic concentration of 200 ng/ml. The incidence of side effects increased with increasing plasma concentrations. CNS effects at high concentrations included amnesia, confusion, dizziness, depersonalization, and somnolence.

In two studies performed by Bullock and Merchant (8,44), the effects of CP-101,606 were examined in approximately 70 subjects with mild, moderate, or severe head injury or hemorrhagic stroke. These studies were open label and, given the small numbers of subjects, where not designed to detect improved outcomes. CP-101,606 infusions were from 2 to 72 h. Serum concentrations of study drug were generally maintained well above 200 ng/ml. Cerebrospinal fluid concentrations of the compound were also maintained above this level. CP-101,606 was well tolerated, with no adverse events attributed to study drug in any subject. It was interesting to note that in subjects with severe head injury, those receiving 2-h infusions (which are unlikely to be therapeutic) had outcomes similar to historical controls with an approximate death rate of 30% and a score on the Glasgow Outcome Scale of “good” in about 10% at 6 months. However, 9 of 11 subjects receiving 24–72-h infusions of CP-101,606 had a score on the Glasgow Outcome Scale of “good” with no deaths. Given the limitations of the study, these results are sufficiently intriguing to support more definitive studies. A multi-center, double-blind, placebo-controlled study in severe head injury in approximately 400 subjects is now ongoing.

**CONCLUSIONS**

CP-101,606 is a potent and selective antagonist of the NR2B subtype of NMDA receptors. It is a highly soluble agent with excellent brain exposure after peripheral administration. In a variety of in vivo studies, CP-101,606 has been shown to have neuroprotective effects associated with plasma concentrations of 200 ng/ml. In the clinic, initial safety studies in normal volunteers confirmed an acceptable separation between the predicted efficacious plasma concentration and those associated with side effects. Safety and tolerability studies in head-trauma patients confirmed the safety of the compound in compromised patients. Preliminary findings in trauma patients suggest that 72-h treatment with CP-101,606 decreases morbidity and improves outcomes at 6 m. These encouraging
results support further clinical evaluation of CP-101,606 in an expanding range of conditions.

REFERENCES


