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NPS 1506, a moderate affinity uncompetitive NMDA receptor antagonist: preclinical summary and clinical experience

Short Comment

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Summary. NPS Pharmaceuticals, Inc. (NPS) has synthesized a series of open-channel blockers with varying potencies at the NMDA receptor. NPS 1506 (Fig. 1) is a moderate affinity antagonist that inhibits NMDA/glycine-induced increases in cytosolic calcium in cultured rat cerebellar granule cells (IC_{50} = 476 nM) and displaces the binding of [^{3}H]MK-801 to rat cortical membranes (IC_{50} = 664 nM).

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Further studies in the rat cerebellar granule cell preparation demonstrate that the block produced by NPS 1506 is uncompetitive; the degree of inhibition at any given concentration of NPS 1506 is increased as the concentration of agonist (NMDA) is increased. The action of NPS 1506 in *Xenopus* oocytes is use- and voltage-dependent, consistent with open-channel block. NPS 1506 was nonselective against cloned NMDA receptors expressed in *Xenopus* oocytes, with equal potency at NR2A, NR2B, ε3 (NR2C) and ε4 (NR2D) subunits. MK-801, in contrast, was more potent at NR2A and NR2B subunits.

The neuroprotective activity of NPS 1506 has been demonstrated in a variety of *in vivo* models of focal ischemic stroke, hemorrhagic stroke, and head trauma. Neuroprotective activity was shown when treatment was delayed 2 hours after the onset of ischemia in two rat models of temporary focal ischemia, demonstrating a 2-hour window of opportunity in these models. Neuroprotective doses of NPS 1506 ranged from approximately 0.1 to 1.0 mg/kg. Doses were more effective when administered twice, 4 hours apart.

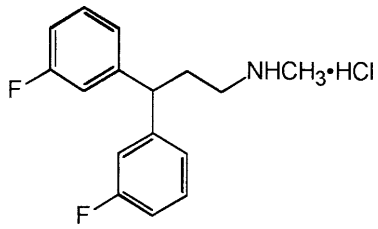

Fig. 1. Chemical structure of NPS 1506

A loading dose plus constant-rate infusion regimen provided neuroprotection in a model of temporary focal ischemic stroke. Peak plasma concentrations following neuroprotectant doses were between 8 and 80 ng/ml.

A number of experiments were carried out to demonstrate that NPS 1506, like the other moderate affinity uncompetitive channel blockers discussed by other speakers previously, does not elicit PCP-like behavioral effects. First, the administration of NPS 1506 to rodents at doses up to 10 mg/kg i.v. did not elicit the side effect profile that is typical of potent open-channel blockers. Specifically, MK-801-like behaviors such as backwards shuffling and head weaving were not noted. Second, NPS 1506 at doses up to approximately 5 mg/kg i.p. did not generalize to PCP in rats trained to discriminate PCP from saline. Third, NPS 1506 at doses up to 10 mg/kg i.v. did not elicit neuronal vacuolization in rats. Fourth, NPS 1506 at doses up to 10 mg/kg p.o. did not impair pre-pulse inhibition of startle in rats. Finally, NPS 1506 at doses up to 3.3 mg/kg i.v. did not produce a lasting impairment of spatial learning in the rat Morris water maze task. In each case cited above, the dose listed was the highest dose examined; increasing the dose further led to side effects, e.g., whole body tremor, that interfered with the experiment.

NPS 1506 was examined in a series of GLP-compliant intravenous toxicology studies ranging from single dose studies to 14-day studies. NPS 1506 was administered intravenously to rats and dogs either as a slow (60-second) bolus or by continuous infusion. The predominant, consistent findings in the single-dose, 60-second bolus and 24-hour infusion intravenous studies in rats and dogs involved transient central nervous system (CNS)-related events that consisted of whole body tremors (convulsions at high doses), hypertonia, salivation, emesis, hypothermia (rats), hyperpyrexia (dogs), vocalization, and death. The severity and duration of these effects were dose-related but independent of the dosing regimen. A very consistent finding in both rats and dogs was the appearance of tremor at plasma concentrations of 400 ng/ml and above. Similar findings were obtained in 7-day and 14-day repeated bolus-dose studies and continuous infusion studies. Other than an irritation/inflammation at the injection site at the higher doses in the 7- and 14-day studies, there was no histopathological evidence of target-organ toxicity elicited by NPS 1506 in any of these studies.

The initial Phase I study of NPS 1506 was a double-blind, placebo-controlled, ascending-dose tolerability and pharmacokinetic study in healthy

male volunteers (age 18–40, weight 60 to 90 kg). NPS 1506 was administered as a single intravenous infusion at rates ranging from 1.0 to 2.67 mg/min. Doses of NPS 1506 from 5–100 mg were well tolerated and provided plasma concentrations covering the 8–80 ng/ml range required for neuroprotection in rodents. Adverse events noted at the 100 mg dose included mild dizziness and lightheadedness, and mild to moderate ataxia. Importantly, neither PCP-like psychotomimetic effects nor cardiovascular effects were noted. NPS 1506 has a very large volume of distribution at steady-state (V_{ss}) of approximately 17 L/kg, consistent with extensive distribution throughout the body. The long terminal plasma half-life (~60 hr) suggests that a single i.v. dose will be sufficient to provide prolonged neuroprotection.

Patient enrollment and dosing has been completed in a double-blind, placebo-controlled, ascending-dose Phase Ib safety and pharmacokinetic study in 36 stroke patients. Male and female (non-pregnant, non-lactating) patients between the ages of 18 and 80, with the onset of stroke within 48 hours prior to dosing, and an NIH Stroke Scale score between 2 and 15 at presentation were dosed with NPS 1506 (60, 80, or 100 mg, infused over 60 minutes). NPS 1506 was well tolerated at all three doses, and there were no serious adverse events associated with NPS 1506.

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