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Minocycline for Acute Neuroprotection

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Abstract

Minocycline is a widely used tetracycline antibiotic. It has been used for decades in the treatment of various gram-positive and gram-negative infections. More recently, minocycline has been shown to have neuroprotective properties in different animal models of acute neurological injury. As a neuroprotective agent, minocycline has the potential to be superior to most of the previously tried agents. In addition to its high blood-brain barrier penetration, minocycline is also a safe compound commonly used in chronic infections. Its multiple mechanisms of action (anti-inflammatory, antiapoptotic and protease inhibitor) in neuroprotection make it a desirable candidate therapy for acute neurological injury, such as ischemic stroke. Minocycline is ready for clinical trials in acute neurologic injury.

Keywords

Minocycline; Stroke; neuroprotection

Numerous studies have been conducted in the hope of developing an effective neuroprotective agent for acute brain injury, particularly ischemic stroke. To date, no pharmacologic agent has been shown to be efficacious in a context of acute intervention. It is likely that agents like calcium channel blockers and glutamate antagonists did not show benefit in acute brain injury for several reasons and may include: poor blood-brain barrier penetration; dose limiting toxicity of the agent;[1–4] and the time-window in which the drug was effective was not long enough to be translated readily into clinical use.[3–6] After careful review of the failed studies, it is clear that there is a need to investigate new approaches to acute brain injury. This review discusses how minocycline differs from failed agents, the mechanisms of its acute neuroprotective effect, and the pharmacokinetic and toxicity information necessary to use minocycline for acute neuroprotection in humans.

Background

Minocycline is a widely used semi-synthetic tetracycline antibiotic[7] with known anti-inflammatory, anti-apoptotic and glutamate–antagonist properties in several models of brain injury. As an anti-infective agent, it has been used for decades to treat infections caused by a variety of gram-negative and gram-positive organisms. Minocycline is indicated for several

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diseases including acne vulgaris,[8] CNS and UTI infections, gonorrhea, meningitis, shigellosis, conjunctivitis, psittacosis, Q fever, relapsing fever, syphilis and others. Minocycline is a generic drug that has been used in humans as oral or intravenous formulations and subgingival sustained release microspheres (Arestin) are used in adult patients with periodontitis.[9] In bacteria, minocycline, as other members of the tetracycline class of compounds, acts by interfering with protein synthesis through binding to the 30S ribosomal subunit, which results in inhibition of mRNA/tRNA interaction and protein translation.[10] However, evidence supporting the anti-inflammatory actions of the tetracyclines, aside from the anti-bacterial properties, has emerged in recent years.[11,12] Due to its anticollagenase, immunosuppressive and immunomodulating effects, minocycline HCl has been used for the management of rheumatoid arthritis.[13]

Neuroprotective properties of minocycline

Over the last 5 years, there have been a large number of reports demonstrating the efficacy of minocycline in a variety of animal models of acute neurological injury (Table 1).[14–24] These studies demonstrate that minocycline has a broad neuroprotective effect, unrivaled by other agents. Minocycline is effective in animal models of global cerebral ischemia,[18,19] focal cerebral ischemia,[14,17,25] traumatic brain injury (TBI),[23] spinal cord injury (SCI),[20–22] and intracerebral hemorrhage (ICH)[24]. All these injuries share some common pathophysiological mechanisms and the need for ultra-early (probably within 3–6 hours of onset) interventions and treatment. There is not only reduction in tissue injury but there is also improvement in functional recovery with minocycline treatment.

Minocycline is likely to be more successful than other studied neuroprotective compounds in that it avoids all of the common pitfalls stated above. It has been shown to demonstrate superior blood-brain barrier penetration[26] and be protective at an extended time window (greater than 3 hours) in experimental animals.[14,17,24] In addition, since it is a safe compound, it is particularly well suited to a clinical trial. Minocycline appears to be an ideal candidate to overcome the issues identified in the previous failed neuroprotective trials.

Mechanisms of action of minocycline as neuroprotective agent

Anti-inflammatory effects

The anti-inflammatory actions of tetracyclines have been demonstrated in both acute and chronic brain injury. Minocycline has anti-inflammatory effects on neutrophils, monocytes, microglial cells, and neurons. Minocycline inhibits neutrophil-mediated tissue injury via inhibition of neutrophil migration and degranulation, as well as suppression of oxygen-radical formation.[27] In a focal cerebral ischemia model, minocycline inhibits enzymes that contribute to inflammation such as the inducible form of nitric oxide synthase (iNOS) and Interleukin-1beta-Converting Enzyme (ICE-1),[18] suppresses apoptosis, and reduces microglial activation.[14,18] Minocycline inhibits nitric oxide (NO) release (likely due to suppression of NOS expression) from monocytic cells induced by lipopolysaccharide (LPS) or interferon-gamma expression.[28,29] In an acute toxin model of Parkinsons disease, minocycline protected neurons (induced by MPTP, an oxygen radical based mechanism of injury) where inflammation contributes prominently to neuronal injury. In this model, minocycline prevented microglial activation and expression of Interleukin-1 (IL-1) and iNOS.[30] In a rat model of immune/inflammatory encephalitis (EAE), where microglia, monocytes, and T-cell activation mediate neuronal injury via multiple inflammatory mediators, minocycline delayed and reduced the progression of the disease (including demyelination) as well as inflammatory cell infiltration.[31]

Minocycline at nanomolar concentration inhibits glutamate excitotoxic effects in mixed neuron/glia cell culture correlating with inhibition of p38 phosphorylation and IL-1 release.[32] Minocycline protects rat neurons (cerebellar granule) from excitotoxic injury induced by reactive oxygen species and NO. Minocycline neuroprotection in vitro is associated with inhibition of inflammatory signaling kinases such as p38.[33] In an EAE model, minocycline reduced TNF release from activated oligodendrocytes while enhancing the release of Interleukin-10 (IL-10) (an anti-inflammatory cytokine).[31]

The anti-inflammatory effects of minocycline have also been demonstrated in humans. At doses commonly used in humans for other indications, minocycline was shown to provide anti-inflammatory benefits in rheumatoid arthritis patients that have not been treated by other disease modifying agents.[34,35] Recently, in a small pilot clinical trial in multiple sclerosis, minocycline at a dose of 200 mg daily reduced the number of gadolinium-enhancing lesions on magnetic resonance imaging (MRI)[36], demonstrating its ability to decrease the inflammatory damage associated with the disease. In summary, compelling evidence has been raised in the past few years to suggest that minocycline modulates inflammation and this might represent a novel therapeutic approach to diseases that are characterized by elevation of inflammatory cascades, such as in acute ischemic brain injury.

Anti-apoptotic effect

Apoptosis is thought to play a role in both acute and chronic brain injury. Minocycline has been shown to prevent this programmed cell death (apoptosis) and the release of cytochrome c from mitochondria in a number of in vitro and in vivo models. Minocycline delays progression of Amyotrophic Lateral Sclerosis (ALS)- like syndrome in Superoxide dismutase-1 (SOD-1) mutant mice and inhibits mitochondria cytochrome c release (*in vitro* and *in vivo*).[37] Minocycline inhibits both caspase-dependent (cytochrome c and Smac/Diablo release) and caspase-independent (apoptosis inducing factor release) mitochondrial cell death in a Huntington striatal cell model.[38] Minocycline protects renal proximal tubule cells from apoptosis upon exposure to azide, hypoxia, staurosporine, and cisplatinum.[39] Minocycline induces the upregulation of the anti-apoptotic protein Bcl-2, at the messenger ribonuclease (mRNA) level. In fact, the anti-apoptotic effects of minocycline are lost when the cells are pretreated with bcl-2 antisense suggesting that the anti-apoptotic action of minocycline is dependent upon bcl-2. Moreover, bcl-2 is also upregulated in neurons in vitro when incubated with equivalent doses of clinically therapeutic concentrations of minocycline.[40] In cardiomyocytes exposed to anoxia-reoxygenation, minocycline inhibited the release of cytochrome c and Smac/Diablo from mitochondria and inhibited caspase activation and apoptosis.[41]

Inhibition of matrix metalloproteinases (MMPs)

The tetracyclines are known inhibitors of the MMPs.[42] Low dose doxycycline was the first FDA-approved MMP inhibitor and is used in periodontal disease.[43] In a rat model of adjuvant arthritis, doxycycline and tetracycline (two close analogs of minocycline), in combination with a standard non-steroidal anti-inflammatory agent, reduced joint swelling and inflammation and improved radiological evidence of damage. In this model, the arthritic syndrome was associated with suppression of MMP-2 (gelatinase) activation obtained from the inflamed joints.[44] Minocycline also reduced MMP-9 in an EAE model.[31] In a collagenase-induced ICH model, minocycline reduced MMP-12 and improved functional outcome.[24I] It has also been shown that minocycline reduces renal microvascular leakage in a rat model of ischemic renal injury (IRI). This action is probably due to diminishing the activity of MMPs.[45] MMPs are increasingly being associated with diseases that involve degeneration of extracellular proteins and matrix in the brain[46]. For that reason, the

inhibition of these proteases through minocycline seems to be an attractive experimental therapeutic approach.

Summary of mechanisms of action

Minocycline has multiple mechanisms of action including anti-inflammatory, MMP inhibition and anti-apoptotic that make it an attractive neuroprotective agent. It has activity in multiple acute and chronic animal models of neurological disease. It is one of the few agents that shows efficacy in animal models of spinal cord injury (SCI), traumatic brain injury, intracerebral hemorrhage (ICH), global and focal cerebral ischemia. This points to another key element that distinguishes minocycline from other neuroprotective agents: the diversity of cellular mechanisms affected. Furthermore, it is likely that minocycline may be acting through vascular mechanisms also, which in the past years have been correlated with the intensity of the inflammatory response to injury and severity of damage to the brain parenchyma.[47] Finally, in humans, minocycline appears to exert anti-inflammatory properties at the same dosing regimens that are clinically utilized for anti-bacterial treatment. Therefore, minocycline is a candidate drug for neuroprotection in acute brain injury in its present human formulation and dose.

Pharmacokinetic issues

In acute brain injury, the ability to deliver a potential neuroprotective agent rapidly to the systemic circulation is a necessity, most often requiring intravenous administration. Since minocycline has been used for decades, the clinical pharmacokinetics are well - described In humans. After a 200 mg intravenous dose, peak concentrations are, on average, 4.0 mg/L, [48] and steady-state concentrations after 100 mg orally twice daily for 3 days range from 1.4 – 1.8 mg/L.[26] Minocycline is the most lipophilic of the commonly used tetracycline antibiotics and cerebral spinal fluid (CSF) concentrations of 11 – 56% of plasma concentrations are achieved.[26] Therefore, one would expect CSF concentrations after chronic dosing to be approximately 0.5 mg/L. In addition, minocycline has lower urinary excretion than other tetracyclines, so it is safer to use for patients with renal insufficiency.

Since 1999, most of the published evidence of the neuroprotective effects of minocycline in rodent models of brain injury have employed large intraperitoneal (IP) doses,[14,17,19,23,24,25,39,49,50] ranging from a low of 10 mg/kg to a high of 90 mg/kg.[16,23] Even in stroke models, where timely delivery of neuroprotection to the brain is known to be important, IP administration was used.[14,19,24,39] Since the pharmacokinetics of large IP doses of minocycline in rodents was unknown and necessary in order to translate the experimental research to humans, we performed a study to accomplish this. We found that the IP route resulted in widely variable minocycline serum concentrations and delayed absorption into the systemic circulation, with peak concentrations achieved, on average, 2.5 hours after injection. When compared to intravenous (IV) administration, bioavailability ranged from 10% to 80%, probably due to frank deposition of the drug in the peritoneal cavity.[51] The IP route of administration probably accounts for the wide range of high doses in the literature. Use of IV dosing was needed to determine the “true” therapeutic window and dose-response relationship in focal cerebral ischemia.[51] We have determined that peak serum concentrations above 3.5 mg/L and trough concentration above 2mg/L are neuroprotective in temporary focal cerebral ischemia in rats.[17] Lower doses are currently being tried.

When the absorption problems of both oral and IP administration are overcome by IV administration, the volume of distribution of minocycline is similar in rats and humans when adjusted by weight.[51] In other words, administration of 3 mg/kg IV to humans and rats would be expected to achieve peak concentrations of the same magnitude (3–5 mg/L). The

main difference in the pharmacokinetic parameters between the two species is the half-life, which is approximately 17 hours in humans[26] and only 3 hours in rats.[51,52] In summary, intravenous minocycline, in doses commonly used in humans, should achieve serum and CSF concentrations that have been shown to be neuroprotective in animal models.

Adverse effects of minocycline

Most of the information available on the tolerability of minocycline has been obtained after chronic oral administration. In ambulatory patients taking minocycline chronically, raising the dose beyond 100 mg twice daily has been problematic because of the common (26–78% of patients) side effect of dizziness.[8,53] More recently, all adverse effects of oral minocycline in ALS patients were found to be gastrointestinal (GI) in nature.[54] The average tolerated dose was 387 mg daily and all patients could tolerate at least 300 mg daily. No dizziness was experienced but elevations in blood urea nitrogen and liver enzymes were reported over the 6-month treatment period. Doses of up to 400 mg IV have been used safely for the treatment of serious infections in humans. In a case series of 119 patients receiving from 200–400 mg of intravenous minocycline for 2–24 days for the treatment of infectious diseases,[55] 21/119 (18%) experienced side effects, 50% of which were gastrointestinal in nature. Only one patient discontinued therapy prematurely and this was a patient who developed azotemia and the attribution was complicated by a case of chronic urinary tract infection. In a search of all reported adverse effects with intravenous minocycline reported to the World Health Organization (WHO) Collaborating Center for International Drug Monitoring, Uppsala, Sweden since 1975, 122 case reports of adverse drug reactions were reported. No assessment of causality was given and the report does not represent the opinion of the WHO. The most common event reported was hepatic function abnormality (19 reports). Thrombocytopenia was reported 11 times and one case of injection site reaction was reported. The WHO data is limited by the fact that no denominator can be ascertained and the dose and duration of intravenous minocycline administered is also unknown.

It is still unknown what dose of minocycline will be neuroprotective and tolerable in human patients. In addition, the feasibility of rapidly administering intravenous doses of minocycline to patients and preliminary evidence of activity of the compound should be determined before committing to further development of minocycline as a therapeutic strategy for acute neuroprotection. The question of optimal duration should be addressed through assessment of a biomarker of inflammation and minocycline serum levels in the patient. In addition, further translational studies in experimental animals will contribute to our understanding of the optimal duration of minocycline treatment in neuroprotection.

Conclusion

Minocycline, which is already in clinical trials for the chronic brain injury of ALS and MS, has a strong therapeutic potential for brain diseases that require acute intervention, such as stroke. It has long been established as a safe drug for clinical use, has multiple mechanisms of action and has a delayed therapeutic window in experimental models. Minocycline is ready for clinical trials as an acute neuroprotectant.

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Table 1

Efficacy of minocycline in a variety of animal models of acute neurological injury

Model	Animal used	Dose	Time window	Outcome
Focal ischemia; TMCAo[a] (90 minutes)	Rat	45 mg/kg IP[b] bid x first day; 22 mg/kg IP bid X 2 subsequent days	Pretreat 2 or 4 hours	76% infarct reduction (72 hours) 63% reduction[14]
Focal ischemia; Embolic clot model	Rat	45 mg/kg IP bid X first day 22.5 mg/Kg IP bid X 2nd day	1 hr	42% infarct reduction (48 hours)[15]
Focal ischemia; PMCAo[c]	Mice	90 mg/Kg IP	Pretreat 60 min before or 30 min Post	Reduction in infarction and brain swelling[16]
Focal ischemia; TMCAo (90 minutes)	Rat	3 mg/kg IV and 10 mg/kg IV	4 and 5 hrs	40–50% infarct reduction (24 hours)[17]
Global ischemia	gerbils	45 mg/kg IP 90 mg/Kg IP bidX1st day; 45 mg/Kg after 36 hrs	pretreat 30 minutes post	Increase survival of CA1 neurons from 10% to 77% Increase to 71%[18]
Neonatal Hypoxia- ischemia (Carotid occlusion +hypoxia)	Rat pups	45 mg/kg IP or 22.5 mg/Kg IP	Immediately before before or after hypoxic insult	Robust protection with pre and 30 minutes post but not 3 hours post[10]
SCI[d]	Rat	50mg/kg IP bidX2days	30 min post	Improved functional outcome[20]
SCI	Rat	90mg/kg IP;45mg/Kg IP bidX5 Subsequent days	1 hr post	Enhance long-term hind limb locomotion, coordinated motor function and hind-limb reflex recovery[21]
SCI (Extradural compression with aneurysm clip)	Mouse	50 mg/kg	1 hr post	Improved hind limb function and strength; axonal sparing; superior to methylprednisolone[22]
Traumatic brain Injury	Mouse	90mg/kg IP 45 mg/Kg IP Bid till sacrifice	pretreat or 30 minutes post	Improved functional outcome(Rotarod); decrease in lesion size[23]
ICH[e] (Collagenase)	Rat	45 mg/Kg IP bidX1day; 22.5 mg/Kg IP	1 hour	Improvement in functional outcome[24]

[a] Temporary middle cerebral artery occlusion

[b] Intra-peritoneal

[c] Permanent middle cerebral artery occlusion

[d] Spinal cord injury