

Review Article

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Use of minocycline in viral infections

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Repurposing of old drugs is a useful concept as it helps to minimize costs associated with the research and development of a new drug. Minocycline, a common second generation antibiotic, has been shown to possess several other beneficial effects other than its intended uses. The antiviral role of minocycline has generated considerable interest from the last decade. It was first shown to be beneficial in preventing human immunodeficiency virus (HIV) infections and later it was reported to improve cognitive deficiencies associate with neuroAIDS. However, its antiviral efficacies are not limited to retroviruses alone. In animal models or *in vitro* systems of flaviviral infections (especially Japanese encephalitis virus), minocycline has been shown to be highly effective. However, not all effects are based on direct inhibition of viral replication. The general anti-inflammatory and immunomodulatory properties of minocycline are also responsible in part, in imparting the protective effects. Owing to the fact that minocycline is well tolerated by most people and that the drug has nearly 40 years history of usage, it is an exciting prospect to try out in other viral infections.

Key words Antibiotic - neurodegenerative diseases - viral infections

“The most fruitful basis for the discovery of a new drug is to start with an old drug”.

James W. Black
Nobel Prize in Physiology or Medicine (1988)

Minocycline: from bacterial infections to neurodegenerative diseases

Minocycline is a semi-synthetic second generation tetracycline that has now been in use for more than 40 years. It was synthesized in 1967 by the erstwhile Lederle Laboratories (part of American Cyanamid that was subsequently bought by American Home Products Corp. in 1994 which in turn became a part of Pfizer Inc. in 2009), and became commercially available from 1972 under the brand name of Minocin, after

getting United States Food and Drug Administration (FDA) approval in June 1971. Minocycline was originally developed to treat a wide array of diseases such as susceptible bacterial infections of both Gram-negative and Gram-positive organisms and is currently recommended for the treatment of anthrax (inhalational, cutaneous, and gastrointestinal), moderate-to-severe acne, meningococcal (asymptomatic) carrier state, Rickettsial diseases (including Rocky Mountain spotted fever, Q fever), nongonococcal urethritis, gonorrhoea, acute intestinal amoebiasis, respiratory tract infection, skin/soft tissue infections, and chlamydial infections¹⁻³. Apart from the approved uses, minocycline is being used to treat rheumatoid arthritis⁴ and has even been tried for the treatment of leprosy⁵.

Owing to its relatively small size (495 Da) and highly lipophilic nature, minocycline crosses the blood-brain barrier (BBB) with ease and has been shown to penetrate the cerebrospinal fluid (CSF) of human beings better than doxycycline and other tetracyclines^{6,7}. Owing to these properties it had been suspected that minocycline may play a role in neurological processes. In a landmark study in 1998, Yrjanheikki *et al*⁸ reported that minocycline was neuroprotective in an experimental model of ischaemia. Since then, there has been several reports linking minocycline with neurological diseases such as haemorrhagic and ischaemic stroke⁹, multiple sclerosis¹⁰, spinal-cord injury¹¹, Parkinson's disease¹², Huntington's disease (HD)¹³, and amyotrophic lateral sclerosis (ALS)¹⁴, leading to various clinical trials. Clinical trials of minocycline administration in ALS¹⁵ and HD¹⁶ have been completed with positive outcome and are in progress for traumatic brain injury cases¹⁷. Recently, a double-blinded randomized clinical trial has begun which aims to explore the possibilities of using minocycline as an adjunctive therapy for schizophrenia¹⁸.

Minocycline in viral infections

The earliest available report of antiviral activity of minocycline came when Lemaître *et al*¹⁹ reported in 1990 that it imparts protection against human immunodeficiency virus (HIV) in human acute lymphoblastic T-cell leukemia (CEM) cells. They showed that minocycline (and doxycycline) prevented HIV-mediated cytopathic effects *in vitro*, 7-14 days post-infection. However, during this time frame, virus production was not inhibited, that indicated dissociation between protection against cell death and suppression of virus growth. However, the protected cells could be maintained in culture for 6-7 wk after which there was complete cessation of virus production in the cells, even in the absence of the drug. Later on it was reported that minocycline was also effective in adjunct therapy for acquired immunodeficiency syndrome (AIDS) dementia by virtue of its anti-inflammatory effect on the microglial cells thereby inhibiting their activation and also inhibiting virus production from these cells²⁰. In 2005, a group of investigators from John Hopkins University School of Medicine reported that minocycline imparted significant neuroprotection in a simian immunodeficiency virus (SIV) model of HIV-associated central nervous system (CNS) disease²¹. It was the first report of its kind demonstrating

anti-inflammatory and neuroprotective activity of an antibiotic against a highly pathogenic virus infection and it was also reported that minocycline suppresses HIV and SIV replication in lymphocytes and macrophages, the main target cells, *in vivo*. Minocycline was thus found to be responsible for the reduction of severity of encephalitis, suppressed viral load in the brain, and decrease in the expression of CNS inflammatory markers. Minocycline was also found to inhibit SIV and HIV replication *in vitro*²¹. They went on to show that the protective effect is mediated by the suppression of p38MAPK and JNK levels in the brain thereby leading to inhibition of activation of apoptosis signal-regulating kinase-1 (ASK1)²². Thus it seemed that minocyclines' anti-HIV role is based on its ability to suppress inflammatory reactions in the brain that is associated with the infection. It is also to be noted that minocycline was originally not engineered to target any specific viral proteins. However, a non-clinical, computational docking with molecular dynamics simulation method-based study has proposed that minocycline has a very high predicted binding affinity against HIV-1 integrase²³, the key protein in the integration of the viral DNA into the host genome. Inhibition of the viral integrase could have therapeutic implications, though actual wet lab studies are yet to be performed to evaluate the efficacy of minocycline in such process. It has also been recently reported that the anti-HIV efficacy of minocycline may be attributed to the suppression of cellular activation in human CD4+ T cells²⁴. The study proposes that instead of directly targeting the virus, minocycline acts by altering the cellular environment, thereby placing minocycline in the class of anticellular anti-HIV drugs.

Cognitive impairments associated with HIV infection has been an additional concern. The term 'NeuroAIDS' encompasses those neurologic disorders that are a primary consequence of damage to the central and peripheral nervous system by HIV. The clinical syndromes identified include sensory neuropathy, myelopathy, HIV dementia, and cognitive/motor disorder. It is believed that minocycline, when administered in adjunct to conventional antiretroviral therapy, may help in ameliorating cognitive dysfunctions associated with HIV infection. A recent study²⁵ reports that oral administration of minocycline is effective in alleviating neuronal damage in an animal model of neuroAIDS following infection with SIV. Using proton resonance spectroscopy it was shown that neuronal integrity was maintained following minocycline administration in

SIV infected experimental animals²⁵. These observations are significant in the current context as a clinical trial is currently in progress in Uganda, to evaluate this hypothesis²⁶.

Moving away from retroviruses, it has been shown that minocycline is also effective against flaviviral infections. A study published in 2007 claimed that minocycline significantly inhibited West Nile virus replication in cultured human neuronal cells and subsequently prevented virus-induced apoptosis²⁷. We reported that minocycline was also protective in case of Japanese encephalitis virus (JEV) infection. Using animal models it was shown that this protective role was attributed to reduction in neuronal apoptosis, microglial activation, active caspase activity, proinflammatory mediators released in the brain, and viral titre. Minocycline was also found to be effective *in vitro*, when JEV-infected neuroblastoma cells were protected from virus-induced death²⁸. Minocyclines' antioxidative property has also been shown to significantly ameliorate the oxidative stress generated as a result of JEV infection²⁹ and also imparts protection to the blood brain barrier by decreasing the expression of various adhesion molecules in the brain as well as downplaying the activity of matrix metalloproteinase 9 (MMP-9)³⁰. The observed protective role of minocycline in JE has led to the initiation of a randomized phase II clinical trial to be conducted in Chhatrapati Shahuji Maharaj Medical University (formerly King George's Medical College, Lucknow). The trial has been approved by the Drug Controller General of India and currently going through the preparatory stages³¹.

Fatal encephalomyelitis caused by alphavirus has also been shown to be countered by minocycline. In animal models, minocycline confers protection against alphavirus infection by inhibiting microglial activation in the brain and diminishing production of interleukin 1 beta in the CNS³². However, minocycline's protective action in case of reovirus infections is attributed to its anti-apoptotic activity rather than inhibition of microglial activation³³.

According to an estimate, it takes about 10-15 years of research and nearly US\$2 billion to bring a single new drug to market. Trying out existing drugs for conditions other than what they were originally intended for, is therefore, cost-effective and comparatively easy, as the drugs have approval from regulatory bodies and with known pharmacokinetics and safety profile³⁴. The use of minocycline as an antiviral drug is thus

an ideal case of 'repurposing' an old drug. As seen from the experimental studies, minocycline's antiviral efficacy is mostly based on its anti-apoptotic or anti-inflammatory activities; yet, actual inhibition of viral replication cannot be ruled out. It would also be fruitful to look into other tetracycline derivatives that may have similar activities. It may also be possible in the future to create a network database linking the mechanism of action of all tetracycline derivatives in different viral infections that would create a new vista of antiviral drug research.

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