

Laboratory Research: Tetrandrine, A Novel Anti-inflammatory Compound

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Tetrandrine (TDR) is a natural compound (Mw. 622.7) which can be extracted from a Chinese herbal remedy known as Hanfangji. TDR comes from the specific herb *Stephania Tetrandra* S. Moore of the Menispermaceae family. TDR has a broad spectrum of biomedical properties and few toxic side effects. It has potent antiproliferative and anti-allergic properties.

We have been granted patent protection for the ocular use of this compound, with particular emphasis on therapy for various forms of keratitis and for conjunctivitis. We have studied it in murine models of hay fever conjunctivitis and of herpes simplex keratitis. It is effective in both these models, with both clinical and gene transcriptional indicators of efficacy. It inhibits the immigration of eosinophils into the allergen challenged tissue, and inhibits mast cell degranulation. Further, it inhibits gene transcription of message for production of interleukin 1 beta and for interleukin 5.

In the herpes simplex keratitis model, the corneal damage occurs largely as the result of the exuberant inflammatory response to the presence of virus. Attempts to modify this exuberant response with topical steroids is often met with disastrous consequences. And while TDR is not specifically anti-viral, our studies indicate that it is highly effective at modifying the overly exuberant inflammatory response while not simultaneously impairing elimination of virus or enhancing corneal stromal ulceration. Its primary mechanism of action appears to be on influencing transmembrane signal transduction controlling calcium flux and protein phosphorylation in lymphocytes. In our model of murine herpes simplex keratitis it clearly inhibits corneal infiltration by lymphocytes and other leukocytes, and it suppresses systemic anti-herpes antibody and delayed type hypersensitivity responses. It does not have this result if given simultaneously with corneal inoculation. Rather, unlike the efficacy of anti-viral agents, it produces its maximal benefit if given 7 days after the onset of the corneal infection. Gene transcription of IL-1 beta, IL-6, and tumor necrosis factor alpha are potentially inhibited by TDR. We believe that this inhibition of these major mediators of this inflammation accounts for much of the inhibition of destructive corneal inflammation by TDR.

Conventional treatments of the inflammation accompanying herpes corneal infections are far from satisfactory, and few drugs are known to inhibit IL-1 or IL-6 or TNF-alpha secretion. Corticosteroids suppress mRNA expression and production of IL-1 and TNF-alpha, but the deleterious effects of steroids on corneas infected with HSV are well known. TDR exhibits a dose dependent inhibitory effect on IL-1 and TNF- alpha secretion without significant side effects.

This, along with inhibition IL-6 secretion may be the key to its effectiveness in suppression of corneal damaging inflammation without enhancing viral replication or enzyme-mediated stromal degradation. Work is in progress in our laboratories to further develop this agent for clinical use.