

Copper and Copper Lowering Therapy in Medicine

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Wilson's disease, the inherited disease of copper accumulation and copper toxicity, has been the instrument driving the development of anticopper drugs. Our group has contributed development of zinc, now the optimal maintenance therapy for Wilson's disease, and tetrathiomolybdate (TM), for initial therapy of neurologic patients. Zinc acts by inducing intestinal cell metallothionein and blocking copper absorption, and TM acts by forming a tight complex with copper and protein, making the copper biologically unavailable. TM acts quickly, yet preserves neurologic function, in contrast to prior anticopper drugs.

Beyond Wilson's disease we have discovered that lowering body copper with TM has multiple additional potential uses. First, we have shown that TM has potent antiangiogenic effects through inhibition of multiple angiogenic promoting molecules. Because of its antiangiogenic effects, TM has shown strongly positive anticancer effects in multiple animal models, and has shown encouraging results in human cancer clinical trials so far. Second, the copper lowering effect of TM has produced antifibrotic effects in animal models of pulmonary fibrosis and cirrhosis, perhaps through inhibition of the transforming growth factor beta (TGF β) pathway of fibrosis. As a result of these animal studies, a clinical trial of TM in idiopathic pulmonary fibrosis is underway, and a clinical trial in primary biliary cirrhosis is being initiated. Third, the copper lowering effects of TM have produced dramatic antiinflammatory and organ injury preventive effects in multiple animal models. These include concanavalin A induced hepatitis, acetaminophen induced hepatitis, adriamycin induced myocarditis, and an autoimmune model of systemic lupus erythematosus. In these various models, TM inhibits the inflammatory cytokines tumor necrosis factor alpha (TNF α) and interleukin-1-beta (IL-1 β). The potential mechanisms of TM inhibition of inflammation and organ injury prevention in these models is under current study and will be discussed, along with the potential clinical use of TM on fibrotic, inflammatory, and autoimmune diseases.