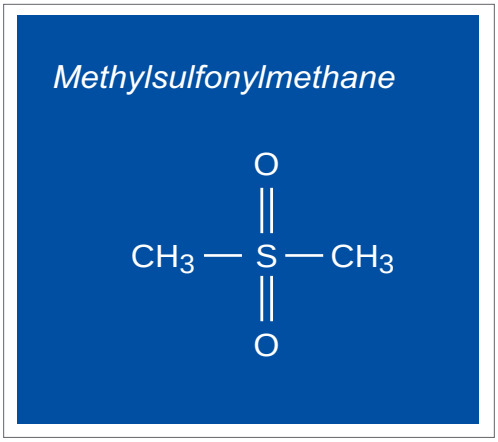

Methylsulfonylmethane (MSM)

Introduction

Methylsulfonylmethane (MSM), also known as dimethyl sulfone ($DMSO_2$) and methyl sulfone, is an organic sulfur-containing compound that occurs naturally in a variety of fruits, vegetables, grains, and animals including humans. A white, odorless, slightly bitter-tasting crystalline substance containing 34-percent elemental sulfur, MSM is a normal oxidative metabolite product of dimethyl sulfoxide (DMSO). Cow's milk is the most abundant source of MSM, containing approximately 3.3 parts per million (ppm). Other foods containing MSM are coffee (1.6 ppm), tomatoes (trace to 0.86 ppm), tea (0.3 ppm), Swiss chard (0.05-0.18 ppm), beer (0.18 ppm), corn (up to 0.11 ppm), and alfalfa (0.07 ppm).[1] MSM has been isolated from plants such as *Equisetum arvense*, also known as horsetail.

Although few human clinical trials have been conducted, MSM has shown therapeutic promise in *in vitro* and animal studies. In addition, MSM has been used with clinical benefit for pathologies for which DMSO, its parent compound, has yielded positive results in clinical trials.

Biochemistry

The natural life cycle of sulfur-containing compounds such as DMSO and $DMSO_2$ begins in the ocean where microscopic plankton release sulfur compounds called dimethyl sulfonium salts. These salts are transformed in the ocean into a volatile compound, dimethyl sulfide (DMS), which escapes from the water as a gas, ultimately rising into the upper atmosphere. When DMS is exposed to high-energy ultraviolet light and ozone, DMS is converted to DMSO and $DMSO_2$. Both DMSO and $DMSO_2$ are water soluble, and therefore return to the earth's surface in rainwater, where plants uptake these two compounds into their roots, concentrating it up to one-hundred fold.

A recent study explored the accumulation of MSM in the brain after oral dosing.[2] Using multinuclear magnetic resonance spectroscopy it was observed that MSM crosses the blood-brain barrier (BBB) in significant concentration. The study also revealed that MSM is evenly distributed throughout the brain, including the brainstem, with equal concentrations in both gray and white matter. Other studies confirm MSM crosses the BBB.[3,4]

Pharmacokinetics

A study with Rhesus monkeys on metabolism and excretion of DMSO found the primary metabolite $DMSO_2$ became detectable in serum approximately two hours after ingestion of DMSO. With continued DMSO ingestion, $DMSO_2$ maintained a steady concentration in the serum. When DMSO was stopped after 14 days, the mean $DMSO_2$ concentration declined slowly over the subsequent 96 hours, and only trace amounts were detectable after five days. The decline in serum $DMSO_2$ was linear, and its half-life appeared to be about 38 hours.[5] The authors observed that absorption in these animals was similar to humans, but elimination was quicker in the monkeys. $DMSO_2$ has been shown to persist in the blood up to five times longer than DMSO.

Mechanism of Action

MSM has been proven to have anti-inflammatory and antioxidant mechanisms in an *in vitro* study[6] in which human neutrophils were artificially stimulated to produce oxidative compounds, including hydrogen peroxide, superoxide, and hypochlorous acid. After cell lines were treated with either DMSO or $DMSO_2$, these free radical by-products were decreased.

It has been suggested that polar solvents such as MSM and DMSO have a chemopreventive mechanism that affects the interaction of tumor cells with the host immune response.[7] Researchers examined DNA of DMSO-treated cells and found these polar solvents create DMSO-induced nicks found in the DNA of folded genomes, suggesting these nicks may cause an untwisting of DNA, with resultant transcription of additional genes.[8,9] Additional chemoprevention studies suggest MSM has no effect on cyclooxygenase (COX) activity or PGE_2 activity, and operates on a COX-independent pathway in inducing differentiation.[10]

An early study of DMSO and $DMSO_2$ demonstrates these agents reduce the binding, uptake, and degradation of low-density lipoproteins by cultured fibroblasts.[11] A similar study showed DMSO and $DMSO_2$ caused a dose-dependent suppression of growth and proliferation of cultured aortic smooth muscle and endothelial cells *in vitro*,[12] the more substantial effect occuring in smooth muscle cells. In addition, $DMSO_2$ was a more potent inhibitor of cell growth than DMSO and its effects were more irreversible than the effects of DMSO.

Clinical Indications

Interstitial Cystitis

Direct instillation of MSM into the bladder has been proposed as a treatment for interstitial cystitis (IC).[13] Although MSM has not been tested in clinical trials, DMSO has shown significant clinical success in a double-blind trial.[14] In 1978, the FDA approved a 50-percent dilution of MSM for instillation into the bladder as a treatment for IC. DMSO readily decreases bladder inflammation; however, there are several unpleasant side effects associated with its use, including halitosis and body odor.

Dr. Stanley Jacob, at the Oregon Health and Science University, pioneered treatment with MSM, particularly in IC.[15] He found that patients tolerate MSM treatment much better than DMSO, and with equal efficacy, including inflammation and pain reduction. Dr. Jacob primarily uses intravesicular MSM for treating IC; however, he often combines oral, topical and IV administration.

Allergic Rhinitis

Fifty individuals suffering from seasonal allergic rhinitis were given 2,600 mg MSM in a multi-centered, open-label trial for 30 days.[16] Although no significant changes were noted in plasma IgE levels compared to baseline, allergy symptoms were greatly reduced. By day 7, both upper and lower respiratory symptoms improved and by day 14, energy levels increased significantly.

Chemoprevention

Chemoprevention is a concept that addresses the prevention or regression of tumor growth and promotion. Currently, several chemicals, including MSM, are being investigated as potential differentiating agents. Two studies in the late 1980s conducted in Sprague-Dawley rats demonstrated a significant reduction in the time to tumor onset in rats treated with MSM. In addition, treated groups had fewer poorly differentiated tumors than untreated groups.[17,18]

More recently, an *in vitro* study demonstrated both MSM and aspirin induce terminal differentiation, utilizing COX-independent mechanisms.[10] Although aspirin was used at a low dose in this study, MSM was used in a much higher concentration to achieve a higher level of differentiation. The COX-independent reaction is presumed to be chemopreventive by invoking the activation of gene functions that lead to differentiation, thereby dismantling the cellular capacity for proliferation.

Autoimmune Disease

A study on rats that exhibit spontaneous autoimmune lymphoproliferative disease examined the effects of oral administration of DMSO or $DMSO_2$.[19] Treatment was started at 1-2 months of age, before any sign of disease was imminent. A dose of 8-10 g/kg/day of DMSO or 6-8 g/kg/day of $DMSO_2$ was administered via a drinking water solution. Following treatment, subjects had significantly diminished lymphoid organ enlargement (spleen, thymus, and lymph node weight) and a decrease in antinuclear antibody response compared to water-drinking controls. Lymphadenopathy was nearly absent in the 43-week old group of treated animals.

Other Clinical Indications

Although not well studied, MSM has been used clinically to treat conditions such as snoring, scleroderma, fibromyalgia, systemic lupus erythematosus, repetitive stress injuries, and osteoarthritis.[15] An unpublished, double-blind study by Lawrence et al assessed the use of MSM in degenerative arthritis. At a dose of 750 mg per day, the study group showed an 80-percent improvement after six weeks, compared to 20-percent improvement in the placebo group.[15]

Side Effects and Toxicity

MSM is believed to be non-toxic.[19] A 30-day study that utilized a 2,600-mg per day dosage revealed no side effects.[16] Studies have not examined long-term supplementation with MSM. To date, one study of MSM in rats revealed that oral administration, at a dose of 1.5 g/kg/day for 90 days, did not cause any adverse effects or increased mortality.[20]

Dosage

Oral dosage of MSM is often in the range of 1-3 grams daily; however, up to 18 grams per day have been used under medical supervision.[15]

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