PRECAUTIONS

Because of lack of long-term safety studies, DGL should be avoided by children, pregnant women and nursing mothers.

Those with hypertension, congestive heart failure, arrhythmias, water retention and low potassium and/or magnesium levels should discuss the use of DGL with their physicians and should be certain that any DGL they use is free of glycyrrhizinic acid.

ADVERSE REACTIONS

There are significant adverse effects with licorice extracts containing glycyrrhizinic and glycyrrhetinic acid when used for the management of peptic ulcer disease, including hypokalemia, hypomagnesemia, hypertension, headache, cardiac arrhythmias, water retention and congestive heart failure. DGL, however, should be free of these side effects. There are occasional reports of gastrointestinal side effects, such as diarrhea and nausea.

INTERACTIONS

The excretion rate of nitrofurantoin was found to be significantly higher in patients receiving the drug along with DGL. No interactions with drugs used in the treatment of peptic ulcer disease are known.

OVERDOSAGE

There are no reports of overdosage with DGL.

DOSAGE AND ADMINISTRATION

In Europe, Canada and South Africa, DGL is available as a medicinal preparation called Caved-S. In the U.S., DGL is available as a nutritional supplement in the form of chewable tablets. Typically, those who use DGL for management of peptic ulcer disorders chew from one to four 380-milligram tablets or the equivalent before each meal.

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DHEA (Dehydroepiandrosterone)

DESCRIPTION

Dehydroepiandrosterone, commonly abbreviated as DHEA, is a natural substance produced in the adrenal glands, gonads and in the brain. DHEA is a steroid prohormone and a precursor for both androgens and estrogens. DHEA and its metabolite dehydroepiandrosterone-3-sulfate, or DHEAS, are the major secretory steroidal products of the adrenal gland and the most abundant circulating steroids in the human adult. The ratio of DHEAS to DHEA in serum is approximately 300:1 to 500:1, and the concentration of DHEAS in the serum is approximately 20 times higher than that of any other steroid hormone. It is noteworthy that the

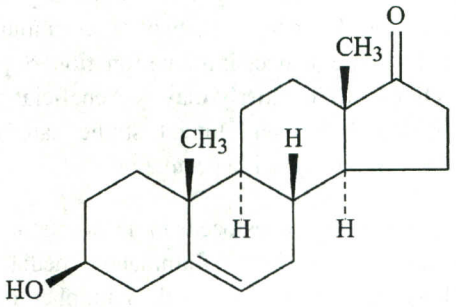
mean concentration of DHEAS in serum decreases progressively from a peak at age 25 to less than 20% of that peak before the age of 70. Further, DHEAS serum levels are typically low in those with chronic diseases, such as cancer and AIDS. While DHEA levels follow a circadian rhythm with a peak in the morning, DHEAS levels are relatively stable throughout the day and therefore are used as a marker for DHEA levels and adrenal androgen secretion.

To date, the unique physiological roles of DHEA and DHEAS remain largely unknown.

DHEA is synthesized in the adrenal cortex in the region known as the zona reticularis. It is produced from cholesterol. Pregnenolone and 17-hydroxy pregnenolone are intermediates, and oxygen and cytochrome P450a17 are involved in the pathway. DHEA itself has weak androgenic activity. It is metabolized in the adrenal gland to other androgenic substances, including androstenediol, androstenedione and testosterone. It is also metabolized to the estrogens, estrone and estradiol. DHEA is converted to DHEAS via a reversible biochemical reaction. DHEA and DHEAS have also been found in the brain, and there appears to be synthetic pathways to their production present in the nervous system. Neurosteroids are steroids that accumulate in the nervous system independently, at least in part, of supply produced by the steroidogenic endocrine glands. These can be synthesized *de novo* in the nervous system from sterol precursors. DHEA and DHEAS in the nervous system are classified as neurosteroids. Neurosteroids include 3-alpha-hydroxy compounds (e.g. pregnenolone, DHEA and DHEAS) and metabolites of progesterone. The expression of the enzyme P450c17 and the biosynthesis of DHEA have been found to interact by way of a tripartite contribution of astrocytes, oligodendrocytes, and neurons. DHEA and DHEAS act as modulators of the gamma-aminobutyric acid type A receptor and of the N-methyl-D-aspartate receptor and may have memory-enhancing, anxiolytic and sleep-inducing (rapid eye movement or REM sleep) properties.

DHEA and DHEAS are being developed by some biotechnology companies as possible pharmaceuticals. Prestara, a synthetic form of DHEA, is an orphan drug for the prevention of loss of bone mineral density in systemic lupus erythematosus (SLE) patients on glucocorticoids. DHEA is also being developed as a possible treatment for systemic lupus erythematosus. Injectable DHEAS is being developed for the possible treatment of acute asthmatic attacks and severe burns. Injectable DHEA is being developed to help preserve neuronal and myocardial tissue from the harmful effects of ischemia/reperfusion injury associated with heart attacks, stroke and cardiovascular surgery. Whether these drugs will prove to be safe and effective and be marketed remains to be seen.

DHEA is known as dehydroepiandrosterone and prasterone. DHEAS is known as dehydroepiandrosterone sulfate, dehydroepiandrosterone-3-sulfate and prasterone sulfate. DHEA has the following structural formula:



DHEA
(Dehydroepiandrosterone)

DHEA can be synthesized in the laboratory from the steroid sapogenin diosgenin, which is extracted from the tubers of the *Dioscorea* wild yam plants, such as cabeza de negro and barbasco. Much of supplemental DHEA is produced in this manner. In fact, these Mexican wild yam extracts served as the starting points for the synthesis of the components of the oral contraceptive pill (OCP).

Extracts of the wild yam plants *Dioscorea mexicana, Dioscorea villosa* or other *Dioscorea* species are not converted to DHEA following their ingestion. Information that markets wild yam as "natural DHEA" is inaccurate.

ACTIONS AND PHARMACOLOGY

ACTIONS

Oral DHEA has weak androgenic activity. DHEA and DHEAS have several putative actions, including anti-inflammatory, anticancer, antiobesity, antidiabetogenic, immunomodulating, memory-enhancing and antiaging.

MECHANISM OF ACTION

Some of the reported effects of oral DHEA may be due to its weak androgenic activity and to the fact that it is metabolized to androstenedione which, in turn, is metabolized to androgens and estrogens. The observed benefits of DHEA in post-menopausal women, for example, may be accounted for by this weak androgenic activity. Administration of DHEA in physiologic doses increases androgens in women, but not in men. Circulating estrogens are increased in both men and women.

DHEA is an inhibitory modulator of the gamma-aminobutyric acid-benzodiazepine receptor complex in rats, and DHEA enhances the effect of excitatory amino acids on the NMDA receptors, also in rats. How this relates to any effect of oral DHEA in humans is entirely speculative.

The decline in the human immune system that occurs with aging is known as immunosenescence. Although not the only factor, an increased cortisol/DHEA ratio appears to be a contributing factor to immunosenescence. The two adrenal steroid hormones appear to have opposing effects on immune function. In general, cortisol is an immunosuppressant, while DHEA enhances immune function. Supplementation with DHEA in the elderly may be beneficial to immune function, although human clinical studies are needed to confirm this. Again, this is speculative.

With aging, several changes occur in inflammatory signaling pathways and in the various inflammatory mediators. These changes have been associated with a number of different degenerative diseases, including cardiovascular disease and neurodegenerative diseases. It has been speculated that DHEA and DHEAS may be able to modulate some of these changes. It has been reported that treatment of human aortic endothelial cells with DHEAS dramatically inhibited the tumor necrosis factor-alpha (TNF-alpha)-induced activation of the major inflammatory transcription factor NF-kappaB and also increased levels of the NF-kappaB inhibitor IkappaB-alpha. It was thought that the peroxisome proliferator-activated receptor alpha (PPAR-alpha) was involved with the inhibition.

In another study, DHEAS, but not DHEA, has been reported to induce peroxisome gene expression via the activation of the PPAR-alpha. Therefore, DHEAS may serve as an important endogenous regulator of hepatic PPAR-alpha-mediated pathways, which maintain lipid homeostasis and prevent the decline in cellular PPAR-alpha expression during aging. There is some evidence that in aging men and women, DHEAS levels are negatively correlated with serum concentrations of the inflammatory cytokine interleukin-6 (IL-6). The increase in IL-6 production during aging might be related to decreased DHEAS secretion. Administration of DHEAS to aging animals has been found to activate PPAR-alpha and reverse the proinflammatory effects of IL-6. Human clinical trials are needed to determine if DHEAS and DHEA have anti-inflammatory activity, and, if they do, by what mechanism. There are some ongoing human studies on the effect of DHEA in systemic lupus erythematosus (SLE), but all of the results are not yet in.

PHARMACOKINETICS

DHEA is absorbed from the small intestine and is transported to the liver, where it is metabolized mainly to DHEAS by the enzyme sulfotransferase. DHEA and DHEAS are distributed to the various tissues in the body where metabolites, including androstenedione, testosterone, estrogens (estrone and estradiol), androstenediol and 7-oxo-DHEA, are synthesized. There is great individual variability in the metabolism of oral DHEA. Excretion of DHEA and its metabolites is primarily via the urinary route.

INDICATIONS AND USAGE

Regarded as a drug by many researchers, a controlled drug in the United Kingdom and a prescription drug in Canada, the use of DHEA as a supplement is not indicated for the treatment or prevention of any condition without qualified medical recommendation and monitoring. The best available research suggests that DHEA, particularly at the high doses many have reported are being used, poses potentially serious health risks.

There is some evidence that DHEA, in monitored doses in selected subjects, may be of some help in easing some of the symptoms of systemic lupus erythematosus (SLE), may enhance immune response in some others and may be indicated in some women with adrenal insufficiency. There is very preliminary evidence that DHEA can have a positive impact on mood and memory. DHEA replacement after menopause has been proposed.

There is no credible evidence that DHEA can burn fat and build lean muscle mass, that it can boost sexual performance or that it can fight cancer, heart disease, fatigue, diabetes, osteoporosis and aging itself.

RESEARCH SUMMARY

Recent research has raised hopes that DHEA may provide some benefit to those with systemic lupus erythematosus (SLE). Studies, both completed and underway, indicate that DHEA, at dose levels that most researchers regard as risky for the general population, enabled some lupus patients to reduce their reliance on prednisone while still achieving equivalent relief from pain, fatigue and inflammation.

In vitro and animal studies have shown that DHEA can inhibit the cytokine molecular signaling that directs release of some of the inflammatory substances implicated in lupus. A synthesized DHEA product called Prestara is currently being tested as a drug for treatment of lupus.

DHEA may have other useful immune-modulating properties. In some studies of immune function in older humans, DHEA has boosted natural killer (NK)-cell activity and has dampened immune-damaging interleukin-6 activity. It has also increased levels of circulating insulin-like growth factor-1 and, when given concomitantly with influenza vaccine, it has boosted antibody titers in an elderly subgroup with particularly low levels of DHEA to begin with. It did not have similar effects when combined with tetanus vaccine. More study is needed to see whether DHEA might be an effective vaccine adjuvant.

DHEA's use in adrenal insufficiency was tested recently in a double-blind study of 24 women with this disorder who were

randomized to receive either placebo or 50 milligrams of oral DHEA daily for four months. These subjects were all DHEA-deficient at baseline. Treatment with DHEA normalized serum concentrations of DHEA, androstenedione and testosterone. Researchers noted a significant correlation between DHEA supplementation and overall "well-being." DHEA-treated women were said to be significantly less depressed and anxious, compared with controls. Sexual thoughts and interest were also found to significantly increase.

Some androgenic effects were observed in this study, but only one subject had to be given a reduced dose of DHEA for this reason. The researchers noted, however, that lower doses in general might be required in the longer-term studies that will be needed to confirm the findings of this preliminary study. They cautioned that DHEA should be used only with medical supervision and carefully monitored to see whether it initiates or promotes breast or prostatic cancer.

In a few aged and severely depressed subjects with diminished baseline DHEA, supplemental DHEA (30 milligrams to 90 milligrams orally each day for four weeks) produced significant improvement. This open-label study involved only six subjects, but some other equally preliminary research, largely confined to animal models, similarly suggests that supplemental DHEA, in some subgroups, might elevate mood and improve age-related declines in memory. One study, however, in which subjects took 100 milligrams of DHEA daily for six months, found no mood-elevating effects. There is no evidence at this time that DHEA is useful in Alzheimer's disease. Recently the DHEA and Well-Ness (DAWN) trial involving 110 men and 115 women aged 55 to 85 concluded that DHEA supplementation has no benefit on cognitive performance or well-being in healthy older adults and stated that "it should not be recommended for that purpose in the general population." This placebo-controlled study used six cognitive function tests. Previous cognitive DHEA tests showed mixed, mostly neutral results; a few showed negative DHEA effects on cognition. In one test, DHEA supplementation was associated with significant impairment on a visual memory recall test. In another test, no DHEA effect was noted on cognition in 46 men aged 62 to 76 during three months of DHEA supplementation.

It has been proposed that DHEA be used (much as estrogen replacement therapy is used) in post-menopausal women to compensate for endogenous age-related and menopause-accelerated declines in DHEA. A dose of 50 milligrams daily has been suggested for this purpose, but there are no clinical trials demonstrating that this regimen would either be effective or safe long-term. It has been noted that DHEA can bring estrogen levels in postmenopausal women to levels equal to that observed in standard hormone-replacement therapy. This may prove risky inasmuch as it has been shown that taking estrogen without concomitant use of progesterone is an established risk factor for uterine cancer.

A number of positive effects have been seen in some DHEA-treated animal models but usually at doses that are considered dangerous in humans. Additionally, these studies have been short-term for the most part, and animal models are considered by many researchers to be poor predictors of human effects since these animals, unlike humans, have little endogenous DHEA and do not exhibit the kind of age-related DHEA declines that are found in humans.

There is no convincing evidence that DHEA boosts sexual performance, retards aging in general or fights cancer and osteoporosis, or that it builds muscle. After 12 weeks of supplementation with DHEA, no improvement was noted in muscle strength in ambulatory myotonic dystrophy type 1 patients. There is one recent study involving old female rats in which DHEA supplementation may have favorably affected insulin sensitivity and may have induced some weight loss. There is also some recent evidence in animal work indicating that DHEA might inhibit chronic hypoxic pulmonary artery hypertension via its effects on smooth muscle cells. Another recent study found an association between lower DHEA plasma levels and risk of impaired endothelial function in postmenopausal women with coronary artery risk factors. There is no evidence, however, that supplementation with DHEA can safely or effectively diminish this risk.

Several studies have failed to find any benefit from DHEA in breast cancer. On the contrary, two studies have found an association between higher levels of DHEA and higher incidence of breast cancer.

Another study has found no correlation between bone density and DHEA levels.

A 19-year follow-up study of nearly 2,000 people reported only a modest decrease in cardiac risk for men and a slight, nonsignificant increase in risk for women associated with DHEA levels. Some small studies have shown that DHEA can inhibit platelet aggregation. But other studies have also shown that supplemental DHEA can lower levels of HDL-cholesterol in some women.

A report in 1988 that high-dose DHEA could favorably affect lipids and induce weight loss in young males was not confirmed in two subsequent trials. In another trial, using the same 1,600-milligram daily dosage of DHEA used in the 1988 study but this time in women, there was, again, no weight loss. The women subjects suffered androgenic effects and developed insulin resistance and adverse changes in lipoprotein.

Other serious adverse effects noted in DHEA studies include transient jaundice and adverse hepatic effects, increased risk of uterine, breast, ovarian and prostate cancers.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

DHEA supplementation is contraindicated in those with prostate, breast, uterine and ovarian cancer. Known hypersensitivity to a DHEA-containing product.

PRECAUTIONS

DHEA supplementation should be avoided by children, adolescents, pregnant women and nursing mothers. The use of DHEA for any health condition should be discussed with one's physician.

ADVERSE REACTIONS

Various androgenic effects, including acne, deepening of the voice, hirsutism and hair loss have been reported in women using supplemental DHEA. Hirsutism and voice changes may be irreversible. There is a report of transient hepatitis associated with DHEA use by a woman. Decreased HDL-cholesterol levels have been reported in women using oral DHEA. This could increase risk of cardiovascular disease. Elevated IGF (insulin-like growth factor)-1 levels have been noted in both men and women taking oral DHEA. Elevated IGF-1 levels have been associated with increased risk of certain types of cancer, e.g. prostate cancer. Oral DHEA has also been observed to increase insulin resistance when taken by women. Manic symptoms and palpitations have been reported with continued use.

INTERACTIONS

DHEA inhibits CYP3A4 *in vitro*, and could increase serum concentrations of the many drugs metabolized by this isozyme.

In some individuals taking alprazolam, or diltiazem, serum DHEA and DHEAS levels may increase. These individuals could be at higher risk of any adverse effects from supplemental DHEA. Danazol, dexamethasone, insulin and morphine may lower endogenous DHEA and DHEAS levels.

DHEA may have additive adverse effects if used along with 4-androstenedione, 4-androstenediol, 5-androstenedione, 19-4-norandrostenedione and 19-5-norandrostenediol

DHEA could have additive adverse effects if used along with testosterone replacement therapy.

OVERDOSAGE

There are no reports of overdosage.

DOSAGE AND ADMINISTRATION

The physiological replacement dose of DHEA is usually considered to be about 25-50 mg/day. Use of DHEA should be discussed with one's physician. Moreover, a physician should closely monitor doses above 50 milligrams daily for any of the possible adverse effects mentioned above.

In March 2007, Senator Charles Grassley introduced a bill in the U.S. Senate (S.762) that that would classify DHEA, if passed, as a controlled substance under the Anabolic Steroid Control Act of 2004. (DHEA had been specifically exempted from the list of controlled anabolic substances.) On December 13, 2007, Senator Grassley introduced the Dehydroepiandrosterone Abuse Reduction Act of 2007 (S.2470). This bill would amend the Controlled Substances Act to impose civil penalties for knowingly selling, causing another to sell, or conspiring to sell a product containing dehydroepiandrosterone to an individual under the age of 18, including any such sale using the Internet. As of September 2008, neither bill has yet been passed.

DHEA is banned by the International Olympic Committee, the National Collegiate Athletic Association, the National Football League and other sports organizations.

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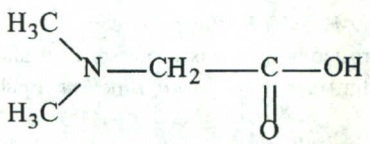
Dimethylglycine (DMG)

DESCRIPTION

Dimethylglycine or DMG is a non-protein amino acid found naturally in animal and plant cells. DMG is produced in cells as an intermediate in the metabolism of choline to glycine.

There has been much confusion surrounding the history of DMG as a nutritional supplement. DMG appeared as a supplement in the 1960s under the names vitamin B15, pangamic acid and calcium pangamate. Calcium pangamate was originally a mixture of calcium gluconate and DMG. Calcium pangamate was intended as a delivery form of DMG. However, several products entered the supplement marketplace called pangamic acid or calcium pangamate, and these did not contain DMG. Some of these products contained, instead of DMG, a substance called diisopropylammonium dichloroacetate. At present, DMG supplements are available that do contain dimethylglycine.

DMG-containing calcium pangamate was popular with Russian athletes and cosmonauts because it was reputed to enhance oxygenation at the cellular level, reduce fatigue and enhance physical stamina. None of those claims, however, was ever substantiated. DMG is neither a vitamin nor an essential nutrient. DMG is also known as N, N-dimethylglycine, (dimethylamino)acetic acid and N-methylsarcosine. Its chemical structure is:



Dimethylglycine (N,N-Dimethylglycine)

DMG is a solid, water-soluble substance. DMG should not be confused with TMG (trimethylglycine or betaine). TMG is involved in the methylation of homocysteine to form methionine (see Trimethylglycine).

ACTIONS AND PHARMACOLOGY

ACTIONS

There are no known actions of supplemental DMG.

PHARMACOKINETICS

DMG is absorbed from the small intestine and from there transported by the portal circulation to the liver. DMG is metabolized in the liver to monomethylglycine or sarcosine which, in turn, is converted to glycine. Dimethylglycine dehydrogenase, a flavoprotein, is the enzyme that catalyzes the oxidative demethylation of DMG to sarcosine. The methyl group produced in this reaction returns to the one carbon pool at the level of N^{10}-hydroxymethyl-tetrahydrofolic acid. DMG itself is formed from trimethylglycine or betaine. DMG that is not metabolized in the liver is transported by the circulatory system to various tissues in the body.

INDICATIONS AND USAGE

It is too early to say whether DMG might eventually be indicated as an immune enhancer or in the management of autism. It is not indicated as an anticonvulsant, in epilepsy or for any condition characterized by seizures. Nor is it indicated as an energy booster or athletic-performance enhancer.

RESEARCH SUMMARY

Based on claims that DMG is a highly potent "oxygenator" of body/brain tissues, this supplement has been touted as a panacea for years.

Several studies show that DMG has no anticonvulsant value and is thus of no help in epilepsy or other conditions characterized by seizures. Persistent claims that DMG is useful in autism are thus far anecdotal.

Claims that DMG can boost energy and athletic performance have been refuted by human and animal studies. Tests on exercising thoroughbred horses found "no beneficial effects on cardiorespiratory function or lactate production." And male track athletes supplemented with DMG exhibited no significant changes in short-term maximal treadmill performance.

On the other hand, an early finding that DMG can enhance both humoral and cell-mediated immune responses has been fortified by some subsequent research. This animal research needs to be extended to humans.

Early fears that DMG might be mutagenic now appear to be unfounded.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Those with hypersensitivity to any component of the preparation should not use DMG.