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Lysine for the Prevention and Treatment of Cutaneous Herpes Simplex Infections

By Philippe O. Szapary, MD and Michael D. Cirigliano, MD

More than 50% of the world's population has recurrent cutaneous herpes simplex virus (HSV) infections.[1] HSV is now the most common cause of genital ulceration in developed countries,[2] and infection rates continue to rise in Europe and the United States. In the United States, viral subtype HSV-2 seroprevalence has risen from 16.4% (1976-1980) to 21.7% (1989-1991).[2] Although clinical disease is self-limited, infection is lifelong and recurrences can cause significant psychosocial morbidity.

Treatment of cutaneous HSV infections usually involves topical or oral antivirals, along with avoidance of predisposing factors (especially stress, sunlight, and upper respiratory infections). Lysine, one of nine essential amino acids (AA), has gained popularity as a cheap and possibly effective agent in the treatment and prophylaxis of recurrent HSV infections. In fact, when taken orally at doses of 1,000-3,000 mg/d, lysine appears safe and effective in some patients as prophylaxis against recurrent cutaneous HSV infection.

History

L-lysine was first introduced in the United States in 1955 as monohydrochloride salt (LMH), a protein supplement for use in bread and cereal.[3] In 1961, the FDA disallowed the use of LMH as an additive to white bread, diminishing food producers' interest in lysine.[3] However, LMH has been widely used as a protein supplement in farm animal feed (famously in *Jurassic Park*).

In the early 1980s, interest in LMH as prophylaxis for HSV infections increased in both the scientific and popular press with the publication of several positive clinical trials. Currently, LMH is readily available, with estimated sales of more than 100,000 lbs in 1992.[3]

INSIDE

Pharmacology

Free lysine is derived from the digestion of protein in the gut. Free lysine is then taken up by the liver where it is used either in protein synthesis or oxidative catabolism. Most free lysine is stored intracellularly in the skeletal muscle pool. Protein-bound lysine is methylated as a first step in the formation of L-carnitine, a protein used in muscle synthesis.[3] Lysine is unique from the other eight indispensable AAs in that it is the most highly conserved.[3] This means lysine is spared relative to other AAs and catabolized more slowly.

Mechanism of Action

Lysine has been recognized since 1952 as a potent inhibitor of viral replication.[4] In 1958, researchers demonstrated that adding arginine to cultured HSV maintained optimum cell growth.[5] In a landmark experiment, researchers found that omitting arginine from culture media decreased viral proliferation.[6] On the other hand, omitting lysine increased proliferation, and when lysine was added to the culture media, it seemed to inhibit HSV replication. In a later study, newly HSV-infected cells switched from synthesizing more lysine-containing proteins to more arginine-containing proteins.[7] From these studies, it was suggested that arginine may act as an inducer of viral capsid protein synthesis, while a predominance of lysine over arginine may act as a repressor or inhibitor.[8]

Clinical Trials

In addition to the first case report supporting an effect of lysine in 1974,[9] 12 other human studies were found searching the MEDLINE, CINHAL, Alt-HealthWatch, and IBIDS databases. Of the 13 studies, eight were distinct double-blind, randomized, placebo-controlled trials (DBRCT).[1,10-16] The DBRCTs were all published in Western Europe (four trials) or the United States (four trials) between 1974 and 1987. The DBRCTs enrolled between 21 and 119 subjects with herpes labialis alone (three trials), or either herpes labialis or genitalis (five trials). There were no trials on patients with herpes genitalis alone.

Despite their titles, only two of the DBRCTs were exclusive treatment trials lasting four to five days. The other trials were 12- to 24-week prophylaxis trials in patients with at least three recurrences per year. Within the prophylaxis studies, lysine dosages ranged from 624-3,000 mg/d. Some of these trials merit special attention.

The initial excitement about lysine came from Griffith and his colleagues who reported more rapid control of outbreaks and reduced frequency of recurrences in a case series of 45 patients.[8] Later, in a survey of 1,543 patients with recurrent cutaneous HSV, these same investigators found that 84% of lysine-treated patients reported less frequent recurrences.[17] Overall, 88% of subjects felt lysine supplementation was effective in treating their HSV infection. Those results led to the publication of the most recent prophylaxis trial.

In this trial, Griffith et al randomized 114 subjects to placebo or LMH 1,000 mg po tid with meals for six months.[10] Although only 52 subjects completed the trial (46% dropout rate), researchers found that the lysine-treated group had 2.4 fewer HSV infections than the placebo-treated group ($P < 0.05$). In addition, lysine-treated patients reported that their lesions healed 2.1 days faster than placebo-treated patients ($P < 0.05$). More importantly, 74% of lysine-treated patients reported their treatment to be "effective" or "very effective" compared to 28% of placebo-treated patients. Problems with this study included the high dropout rate and the lack of intention-to-treat analysis.

These positive results are tempered by three essentially negative DBRCTs by a group of Danish investigators.[11-13] Milman and colleagues found no effect of LMH 1,000 mg po at the onset of symptoms, followed by 500 mg bid for the following four days in the treatment of early cutaneous HSV infection in 119 patients.[13]

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Table 1

Comparison of currently available oral prophylactic therapies for cutaneous HSV infections

Product	Dose	Monthly Cost*
L-lysine (LMH)	500 mg 2 tablets po tid	$11
Acyclovir (Zovirax®)	400 mg 1 tablet po bid	$113
Valacyclovir (Valtrex®)	1,000 mg 1 tablet po qd	$109
Famcyclovir (Famvir®)	250 mg 1 tablet po bid	$95

*Based on Average Wholesale Price

Later, in a prophylaxis trial, 1,000 mg of LMH po qd for 12 weeks also had no effect on recurrences nor rates of healing in 65 patients in a crossover DBRCT.[12] These results were echoed by two other negative prophylaxis DBRCTs done by other investigators.[14,15]

Adverse Effects and Interactions

In the last 10 years, the FDA has become concerned over the safety of AA supplements in the wake of 24 reported deaths in 1988 from eosinophilia-myalgia syndrome linked to a contaminated batch of L-tryptophan.[18] In 1992, the Life Sciences Research Office did not reach a conclusion on the safety of lysine, but stated that its use for HSV suppression was not associated with adverse effects.[3]

Multiple animal studies suggest that large doses of oral LMH have no adverse clinical, hematologic, or pathologic side effects.[3] Some studies done in rat pups have shown that lysine-rich and arginine-poor diets cause growth retardation.[3] Intravenous lysine has been associated with renal toxicity and death in rats at doses greater than 4 g/kg of body weight.[3]

Human studies of LMH have not reported any significant toxicity. At the highest doses of 3,000 mg/d, only a few cases of dyspepsia were noted.[10] However, there is one report of tubulointerstitial nephritis which could have been caused by long-term use of 3 g LMH daily.[19]

There are no reported adverse interactions with LMH. Animal data suggest that LMH is safe in pregnancy and lactation.[3] However, there are no human safety data on LMH in pregnancy or lactation.

Formulations and Dosing

LMH is readily available at pharmacies and health food stores as a generic preparation, usually sold as 500 mg tablets. Based on currently available data on prophylaxis, at least 1,000 mg of LMH should be taken daily. The data definitely suggest a dose-response relationship; a dose less than 1,000 mg was not effective in two studies,[15,16] while doses of 1,248 mg and 3,000 mg appeared to decrease recurrences in two studies.[10,16]

Lysine can be found as part of combination preparations that often include echinacea and goldenseal. There are no published clinical trials on any lysine combination products. Topical lysine preparations have been studied in animals, but the benefits shown in animals have not been confirmed in human trials.[20]

Conclusions

Currently available data suggest that LMH is not effective in the treatment of acute cutaneous HSV infections. In acute infections, oral antivirals have proven efficacy, while the data for topical antivirals are less impressive.[21]

For prophylaxis, supplemental LMH at doses between 1,000-3,000 mg/d may decrease the frequency of recurrences. Even negative trials identified subgroups of patients who were particularly responsive to this intervention. Unfortunately, the available studies do not further characterize this group of responders. The oral antivirals shown in Table 1 are effective, and have been approved by the FDA for use as prophylactic agents. LMH, taken three times daily, is cheaper and has fewer side effects than oral antivirals. Increasing consumption of high lysine containing foods, such as meat, milk, fish, and eggs, has never been demonstrated to decrease recurrences.[22] Long-term use of oral antivirals, however, raises the possibility of the development of HSV resistance.

Recommendations

Patients with more than three outbreaks of cutaneous HSV per year may want to consider a trial of LMH, 1,000 mg po tid with meals as a non-toxic dietary supplement to decrease the frequency and severity of HSV infections. Patients with frequent outbreaks should avoid foods known to have a high arginine content such as chocolate, nuts, peas, and cereals. ❖

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L-Carnitine for Treatment of Ischemic Heart Disease, Congestive Heart Failure, and Peripheral Vascular Disease

By Ernie-Paul Barrette, MD

DIETARY SUPPLEMENTS INCLUDE A LARGE GROUP OF amino acids, cofactors, and biochemical intermediates. L-carnitine, an essential cofactor, has been studied for 20 years as a treatment for cardiovascular diseases. Preliminary evidence suggests it may be beneficial.

Myocardial carnitine levels in patients with ischemic heart disease, congestive heart failure (CHF), and cardiomyopathy are reduced compared to normal patients.[1]

Origins

L-carnitine is found in meats and dairy products. Endogenous synthesis in the liver and kidney from lysine and methionine provide adequate amounts in vegetarians. Skeletal and cardiac muscle contain 98% of the body stores.

Biochemistry

L-carnitine plays a critical role in fatty acid oxidation as a cytosol mitochondria shuttle. Carnitine combines with long-chain acyl coenzyme A (CoA) yielding CoA and acyl-carnitine. The acyl-carnitine is transferred into the mitochondria by carnitine translocase where acyl CoA and carnitine are regenerated.

Mechanism of Action

During ischemia, long-chain acyl carnitine rapidly accumulates in the cytosol and acyl CoA levels rise in the mitochondria, while carnitine and ATP levels fall. High levels of long-chain acyl carnitine disrupt multiple membrane-bound enzymes (e.g., sodium potassium ATPase), damage lipid membranes, and uncouple oxidation-phosphorylation. In multiple animal systems, L-carnitine will decrease levels of long-chain esters and reduce injury during ischemia.[2] In addition, carnitine will react with acetyl CoA in the mitochondria and shuttle acetyl carnitine to the cytosol, thus reducing the acetyl CoA/CoA ratio. Since high ratios will inhibit pyruvate dehydrogenase, the rate limiting step in glucose oxidation, carnitine appears to support glucose oxidation and limit lactic acid production.

History

Primary myopathic carnitine deficiency was first described 25 years ago. A progressive painless proximal weakness is seen. Cardiomyopathy may also be present. A systemic form presents with weakness and hepatic encephalopathy. These very rare disorders are seen in infants and children. In 1986 the FDA approved L-carnitine for use in primary carnitine deficiency. By 1980 interest in carnitine therapy for cardiovascular diseases had begun. Much has been published since, although almost all research has been in Europe, and primarily in Italy.

Secondary carnitine deficiencies occur with chronic TPN, dialysis, and valproic acid use. Carnitine supplements have been studied in these conditions as well as for chronic fatigue syndrome, hypercholesterolemia, AIDS, and enhancement of athletic performance. Some studies have used the free radical scavenger propionyl-L-carnitine (PLC). With the exception of studies of dialysis patients, however, data are very limited.

Clinical Studies

Ischemic Heart Disease. Ten trials have reported carnitine to benefit patients with angina pectoris. All of these trials have severe limitations. Sample size was 12 to 44 in all but one trial. A placebo arm was used in six, subjects were randomized in six, and only three were double-blind, randomized, controlled trials (DBRCT).

In the largest DBRCT, Cherchi studied 44 men with chronic stable angina in a crossover trial. Subjects received L-carnitine (1 g/d) or placebo for four weeks. Subjects taking carnitine showed significant improvements in mean exercise work load, watts to onset of angina, and ST segment depression.[3]

The only large trial randomized 200 patients with chronic stable angina to L-carnitine (2 g/d) or usual care for six months.[4] Carnitine significantly improved exercise tolerance measured during cycle ergometric testing. More treated patients entered NYHA class I and were able to discontinue cardiac medications. However, lack of blinding and placebo may have biased the results.

L-carnitine has been studied in post-infarction patients. In an open trial, Davini et al followed 160 post-infarction patients for one year.[5] Subjects were randomized to L-carnitine (2 g bid) or usual care. A remarkable decrease in mortality was seen with carnitine (1.2% vs. 12.5%, $P < 0.005$). However, this study has several problems. Lack of blinding may have influenced patient care. More patients with hypertension were in the control arm (27.8% vs. 17.6%) which may have contributed to their poorer outcome. Also, no information is provided regarding how many subjects received specific therapies (e.g., aspirin, beta-blockers, or ACE inhibitors).

The CEDIM trial also studied patients after a first anterior myocardial infarction.[6] This multicenter DBRCT treated 472 subjects with either L-carnitine (9 g IV daily for five days then 6 g/d) or placebo for 12 months. Carnitine significantly attenuated left ventricular dilation. The increases in end-systolic and end-diastolic volumes were significantly lessened by carnitine. The incidence of death or CHF was 6% with carnitine vs. 9.6% with placebo (P = NS). However, only 8% received an ACE inhibitor and 35% a beta-blocker.

Congestive Heart Failure. Urinary carnitine excretion is increased in CHF.[7] A DBRCT studied 60 patients with CHF (ejection fraction < 50%, NYHA class II or III) for 180 days.[8] Subjects received either PLC (50 mg tid) or placebo. During the study only digoxin and diuretics were allowed. Significant improvements in maximum exercise times and ejection fractions were reported (e.g., ejection fraction 41% to 47%). Two other small trials reported similar results. However, a recently completed, unpublished large-scale trial of PLC in CHF failed to show an improvement in exercise capacity.[9]

Peripheral Vascular Disease. Muscle biopsies in patients undergoing revascularization for peripheral vascular disease (PVD) demonstrated lower carnitine levels compared to controls.[10] A double-blind crossover trial with 20 men compared carnitine (2 g bid) and placebo for three weeks in random order.[11] Carnitine significantly increased treadmill walking distances to claudication compared to placebo (306+/-122 m vs. 174+/-63 m, $P < 0.01$).

The same group reported a DBRCT of PLC vs. placebo for six months (n = 245).[12] After two months, if the maximum walking distance had not improved more than 30%, then the PLC dose or placebo was increased. In a double-blind protocol, the PLC and placebo doses were titrated up every two months from 1 g/d to 3 g/d based on treadmill results. Maximum walking distance was significantly improved with PLC (PLC: from 214.6 m to 354 m vs. placebo: from 207.8 m to 298.1 m, P = 0.03). A non-significant improvement in initial claudication distance, a more reliable outcome than maximum walking distance, was seen with PLC.

Adverse Effects

Carnitine infrequently causes nausea, pyrosis, dyspepsia, and diarrhea. High doses have resulted in a body odor like rotting fish. A myasthenia gravis-like syndrome was seen in dialysis treated patients receiving dl-carnitine but not with L-carnitine. No drug interactions were reported.

Formulation and Dosage

L-carnitine is readily available. Prices vary dramatically, although 60 capsules of 500 mg L-carnitine is available via mail-order catalogs for less than $15. Most marketers suggest 1-2 g/d, which was the dose used in most studies. The CEDIM study used 6 g/d, which would be quite expensive even with the least expensive brand (approximately $45 per month). In primary carnitine deficiency, the recommended dose is three 330 mg tablets two to three times a day. The FDA licensed product, Carnitor® (Sigma Tau) is expensive; the average wholesale price for ninety 330 mg capsules is $75.30. Consequently, prescribing Carnitor instead of another supplement brand of carnitine increases the monthly cost of 1-2 g/d from $15-30 to $75-150.

Conclusion

Several preliminary reports suggest L-carnitine and PLC improve exercise tolerance in patients with chronic angina, CHF, and PVD. L-carnitine may also limit post-infarction left ventricular dilation. Reports of adverse reaction and drug interaction are absent. Unfortunately, there are no definitive trials. The best evidence, the CEDIM trial, did not look at a clinical end point. It is also unclear whether L-carnitine provides any benefit beyond well-established therapies, i.e., aspirin and beta-blockers in ischemic heart disease and ACE inhibitors in CHF.

Recommendation

L-carnitine should not replace well-established antianginals, aspirin, ACE inhibitors, and beta-blockers until further data are available. However, physicians may wish to consider its use in patients who are clinically failing while on these medications or in patients who are unable to take them due to contraindications or intolerance. ❖

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Yohimbine for the Treatment of Impotence

By Teresa Klepser, PharmD and Nicole Nisly, MD

IMPOTENCE, ALSO KNOWN AS ERECTILE DYSFUNCTION, IS defined as a male's inability to achieve or maintain penile erection sufficient for satisfactory sexual performance.[1] Available medical therapies include intracavernosal injections of papaverine hydrochloride, phentolamine, or alprostadil; vacuum constrictive devices; vascular surgery; penile prostheses; and sildenafil (Viagra®).[1] The invasiveness of most of these therapies and the expense of Viagra have sent men to physicians and Internet pharmacies to find a more "natural" approach.

Yohimbine, an alkaloid and prescription drug originally isolated from the bark of the *Pausinystalia yohimbe* tree, is found in tropical West Africa and the

Congo.[2] Yohimbe bark and yohimbine are currently available by prescription and via the Internet without a prescription.

Disease Prevalence and Etiology

Impotence is estimated to occur in 10-20 million males and more than one half of the males aged 40 to 70 years old experience some degree of erectile dysfunction.[1,3] Erectile dysfunction may be the result of psychogenic or organic factors, and most commonly organic. Psychogenic factors include sexual anxiety, guilt, fear, or feelings of inadequacy. Organic etiologies include drugs and disease states such as diabetes, hypogonadism, hypertension, vascular disease, hypercholesterolemia, and neurogenic disorders.[1]

Drug Properties

Yohimbe has been used historically as an aphrodisiac, but also is claimed to exhibit beneficial properties in the management of dysmenorrhea, hypertension, fevers, leprosy, coughs, antidiuresis, and as an anesthetic.[2,4] The yohimbe bark also possesses hallucinogenic properties that become apparent when smoked.[5]

Mechanism of Action

The physiology of erection is based on heightened cholinergic activity, resulting in increased penile blood inflow. Yohimbine, the predominant active ingredient in yohimbe bark, is a centrally-acting alpha$_2$-adrenoreceptor blocker similar to reserpine. Yohimbine stimulates the release of norepinephrine, increasing cholinergic activity and decreasing adrenergic activity.[6] Yohimbine is also believed to inhibit the enzyme monoamine oxidase (MAO) which blocks intracellular metabolism of norepinephrine, serotonin, and other biogenic amines, resulting in increased amine concentration in nerve terminals.[4,5] Yohimbine appears to have no effect on testosterone levels.[7]

Clinical Trials

In the 1960s, several studies were conducted to evaluate the efficacy of Afrodex® for the treatment of impotence.[8,9] Afrodex contained 5 mg of yohimbine, 5 mg of methyltestosterone, and nux vomica extract which contains the active ingredient strychnine. Afrodex was shown to be beneficial in the treatment of impotence; however, it was unknown if one or all three of the ingredients offered benefit in the treatment of impotence.[8] Two of the three components of Afrodex—yohimbine and strychnine (contained in nux vomica)—were banned in nonprescription drugs by the FDA in 1989.

Eventually, yohimbine was studied as monotherapy for the treatment of impotence. Ernst et al performed a meta-analysis of the double-blind, randomized, placebo-controlled clinical trials (DBRCT) that evaluated the efficacy of yohimbine in men with some form of erectile dysfunction.[10] Studies were excluded if the Jadad scale assessing methodological quality was less than 3 out of 5 possible points for randomization, placebo control, double-blind, withdrawals and dropouts accounted, and validated outcomes.[11] Seven trials met criteria and are summarized in Table 1.

Sample size ranged from 11 to 100 males with erectile dysfunction. Cause of erectile dysfunction varied among studies and included organic, psychogenic, mixed, or unknown. Doses of yohimbine ranged between 15 to 30 mg/d. End points were primarily assessed subjectively through self-reported improvement of sexual function. Overall, studies found yohimbine to be beneficial in erectile dysfunction with five of the studies showing a statistically significant difference compared to placebo. The calculated odds ratio (OR) was 3.85 (confidence interval [CI] 2.22 to 6.67), favoring yohimbine over placebo. Side effects were reported in five of the seven studies. The frequency of side effects ranged from 10-30% depending on the study and included hypertension, rash, anxiety, dizziness, increased urinary frequency, gastrointestinal disturbances, and lack of energy. Eight patients withdrew because of serious adverse effects.

Some criticisms regarding the meta-analysis include the variety of erectile dysfunction etiology, age differences between studies, lack of intention to treat analysis, the use of subjective end points, and lack of adverse effects reported. These criticisms weaken the value of these studies regarding efficacy.

No studies evaluating the efficacy of the plant yohimbe have been published.

Adverse Effects

Since yohimbine penetrates the central nervous system in doses lower than those required for peripheral alpha-blockade, side effects may include antidiuresis and central excitation (i.e., agitation, tremors, insomnia, anxiety, sweating, hypertension, tachycardia, nausea, and vomiting).[12-14] There is a case report of 42-year-old black man who developed erythrodermic skin eruption, renal failure, and lupus-like syndrome after ingesting 5.4 mg of yohimbine three times daily for one day.[15] Overdoses of 20-30 mg/d have produced symptoms such as excessive salivation, piloerection, mydriasis, hypo- or hypertension, and death.[6,12]

Contraindications/Precautions

Yohimbe is not recommended for use in individuals

with hypertension, diabetes, heart disease, and liver disease.[16,17] Yohimbe may exacerbate psychoses in schizophrenic patients.[16,17] Yohimbine is contraindicated in pregnancy, pediatrics, psychiatric illness, patients with renal disease, and cardiac or renal patients with a history of gastric or duodenal ulcer.[2,6,18]

Drug and Food Interactions

Yohimbe should not be taken with tyrosine or phenylalanine or with any tyramine-containing food such as cheese, chocolate, beer, aged meats, and wine.[5] The combination of yohimbe and tyramine may raise blood pressure.[5] It is also not advised to take yohimbe or yohimbine concurrently with antidepressants, sedatives, antihistamines, caffeine, or amphetamines.[5,14] The mechanism of action of clonidine is nearly opposite to that of yohimbine; therefore, clonidine may reverse the effects of yohimbine.[2]

Regulation

The German Commission E, the American Urological Association, and the FDA do not recommend the use of yohimbine for the treatment of organic erectile dysfunction.

Yohimbe has been used in Germany for the treatment of sexual disorders, feebleness, and exhaustion.[12] However, the German Commission E does not recommend its use because of the high risk-benefit ratio.[13] Yohimbine is not recommended by the American Urological Association for the treatment of organic erectile dysfunction because the outcome data indicate a marked placebo effect.[18]

In 1989, the Food and Drug Administration (FDA) banned the sale of all nonprescription aphrodisiac drug products due to a lack of efficacy and safety.[19] Ingredients that were banned in non-prescription aphrodisiac products until safety and efficacy could be provided include estrogens, strychnine, yohimbine, mandrake, anise, licorice, zinc, and cantharides such as Spanish fly.

The FDA-approved indications include using yohimbine as a sympatholytic and mydriatic; yohimbine is available as a prescription medication in the United States. Off-label uses for yohimbine in the United States

Table 1

Meta-analysis of seven DBRCTs — yohimbine efficacy in erectile dysfunction

Study	Sample Size	Type of Impotence	Mean Age	Intervention	End Point
Morales	100	Organic	56	Yohimbine 6 mg tid x 10 wks	43 positive response
				Placebo	28
Reid	48	Psychogenic	NA	Yohimbine 6 mg tid x 10 wks	62 improved*
				Placebo	16
Riley	61	Mixed	50	Yohimbine 5.4 mg tid x 8 wks	37 good stimulated erection*
				Placebo	13
Susset	82	Any kind	61	Yohimbine 5.4 mg qid x 4 wks	34 full/partial response*
				Placebo	3
Mann	31	Organic/ non-organic	43	Yohimbine 5 mg tid x 7 wks	60 improved
				Placebo	40
Vogt	86	Unknown	53	Yohimbine 10 mg tid x 8 wks	71 positive response*
				Placebo	45
Rowland	11	Unknown	49	Yohimbine 5 mg tid x 2 wks, 10 mg tid x 2 wks	73 positive response*
				Placebo	9
Meta-analysis	**419**				**Odds Ratio = 3.85 Confidence Interval 2.22 to 6.67**

*Statistically significant difference

NA = not available

Adapted from: Ernst E, Pittler MH. Yohimbine for erectile dysfunction: A systematic review and meta-analysis of randomized clinical trials. *J Urol* 1998;159:433-436.

include the treatment of impotence and orthostatic hypotension.[6]

Formulation and Dosage

Yohimbine tablets containing 5.4 mg of yohimbine hydrochloride are available as standardized prescription medication from various small pharmaceutical companies. A manufacturer's recommended dose of yohimbine is 5.4 mg three times daily. If side effects are experienced, the dose may be decreased to ½ tablet three times daily and gradually increased to one tablet three times daily.[6,14]

Despite being declared an unsafe herb by the FDA, yohimbe and yohimbine may be purchased on the Internet for use as aphrodisiacs or weight loss agents. The herb is available as a single or combination product in tablet, capsule, liquid extract, powder, or tincture formulations. These non-prescription products may contain more than or less than 5.4 mg of yohimbine per dose and may not be standardized.

Conclusions

Traditionally and historically, yohimbe and yohimbine have been used in the treatment of erectile dysfunction. The clinical evidence is weak and the side effect profile is dangerous. Yohimbine may be effective for the treatment of organic erectile dysfunction, but at a steep price.

Recommendation

Yohimbe and yohimbine should not be used in self-treatment.[16,17] Patients should avoid Internet purchases of yohimbe and yohimbine because of the absence of standardization and safe monitoring by some manufacturers. Yohimbine could be cautiously considered in patients who refuse other more invasive or more expensive options and have no contraindications or likely drug or food interactions. All patients who still choose to take yohimbe or yohimbine should be monitored for agitation, tremors, insomnia, anxiety, hypertension, and tachycardia. ❖

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CME Questions

1. **All of the following can precipitate an outbreak of herpes labialis *except*:**
   a. milk.
   b. chocolate.
   c. sunlight.
   d. upper respiratory tract infection.

2. **Based on data from clinical trials, all the following conclusions can be drawn about L-lysine (LMH) *except*:**
   a. One must use at least 1,000 mg/d of LMH to prevent recurrences.
   b. Only oral preparations used three times a day appear effective.
   c. Patients generally believe LMH decreases their lesion frequency and severity.
   d. LMH 1,000 mg per day taken within the first 48 hours of an outbreak will abort the outbreak.

3. **A 70-year-old man suffered an anterior myocardial infarction one month ago. He has severe COPD and developed wheezing after a beta-blocker trial. He refuses to consider cardiac catheterization or surgery. He has had no angina since discharge. For which of the following medications is there no consistent evidence for benefit in the post-infarction patient?**
   a. Aspirin
   b. L-carnitine
   c. Calcium channel blockers
   d. ACE inhibitors

4. **Which of the following has *not* been reported as a side effect for yohimbine?**
   a. Agitation
   b. Sedation
   c. Tremors
   d. Hypertension

5. **Which of the following may reverse the effects of yohimbine?**
   a. Bromocriptine
   b. Aspirin
   c. Clonidine
   d. Atenolol

Letters from Readers

Question: A recent article on *Vaccinium myrtillus* (bilberry) (*Alternative Medicine Alert*, February 1999, pp. 20-21) states that "chronic ingestion or higher doses of bilberry leaf in animals has resulted in cachexia, anemia, icterus, excitation, and death." *Vaccinium myrtillus* is listed as benign in other sources, with no apparent side effects in animals administered up to 400 mg/kg; please provide a reference for these reported adverse effects. *Vaccinium myrtillus* is promoted for small vessel integrity through its collagen stabilizing actions; therefore, it may be useful in progression of ARMD, where we have no really effective conventional treatments.

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Response: *Thank you for your interest in the bilberry article. The source for the Adverse Effects statement is page 311 in* The Complete German Commission E Monographs, *published by the American Botanical Council. There are theoretical reasons why bilberry extract may help macular degeneration, but there is no published clinical evidence to support this claim. Although it is true that the more common form of macular degeneration has no therapy, the minority of patients with the exudative (wet) form do benefit from laser ablation of neovascular membranes. Consequently, I recommend close ophthalmologic follow-up for patients with chronic visual loss.*

Ernie-Paul Barrette, MD
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Clinical Briefs

With Comments from John La Puma, MD, FACP

Fish Oil Supplements for Bipolar Disorder

Source: Stoll AL, et al. Omega 3 fatty acids in bipolar disorder: A preliminary double-blind, placebo-controlled trial. *Arch Gen Psychiatry* 1999;56:407-412.

OMEGA-3 FATTY ACIDS MAY INHIBIT neuronal signal transduction pathways in a manner similar to that of lithium carbonate and valproate, two effective treatments for bipolar disorder. The present study examined whether omega-3 fatty acids also exhibit mood-stabilizing properties in bipolar disorder.

Researchers conducted a four-month, double-blind, placebo-controlled study, comparing omega-3 fatty acids (9.6 g/d) with placebo (olive oil), in addition to usual treatment, in 30 patients with bipolar disorder. Using a Kaplan-Meier survival analysis of the cohort, researchers found that the omega-3 fatty acid patient group had a significantly longer period of remission than the placebo group ($P = 0.002$; Mantel-Cox). In addition, for nearly every other outcome measure, the omega-3 fatty acid group performed better than the placebo group.

Omega-3 fatty acids were well

tolerated and improved the short-term course of illness in this preliminary study of patients with bipolar disorder.

COMMENT

These Harvard, Baylor, and Berlin investigators noted laboratory and animal data which suggest that omega-3 fatty acids dampen "signal transduction pathways associated with phosphatidylinositol, arachidonic acid, and other systems." They tested menhaden fish oil concentrate (a total of 6.2 g of eicosapentaenoic acid and 3.4 g of docosahexanoic daily, in 14 capsules taken in a divided dose daily) against an olive oil placebo. The chief outcome measure was duration of time to exit the trial. The investigators equated exit with treatment failure and worsening of a baseline clinical state.

Forty-four patients with mixed bipolar diseases, varied mood states, and varying medications were randomized; only 30 had evaluable data. Of these, 14 received omega-3s and 16 received placebo. Most of both groups were women; the mean ages were 41 and 45 years respectively. Unfortunately, four dropouts left before the first month was up; 10 more patients did not receive the intervention for the needed four months and were excluded from the final analysis. Eleven fish oil subjects completed the study, but only six placebo did. The discrepancy of an "extra patient" in these latter numbers was not accounted for.

The research, unfortunately, was nearly sunk from the start. A fish oil shortage was documented. Relatively few variables were stratified. The "fishy" aftertaste of fish oil was more often reported in the omega-3 group than the olive oil group. No effort was made to standardize for disease or treatment stage.

Recommendation

It's too early to know whether to recommend fish oil supplements, along with lithium and other medication, to your patients with affective disorders, but if they do take it in this dosage, make sure they subtract 180 calories daily from their diet—14 capsules of oil add up to at least 1.5 tablespoons of liquid fat. In the meantime, fish oil should come from tuna, salmon, mackerel, and herring—fish—instead of capsules. ❖

Anthroposophic Lifestyle and Atopic Disorders

Source: Alm JS, et al. Atopy in children of families with an anthroposophic lifestyle. *Lancet* 1999;353:1485-1488.

INCREASED PREVALENCE OF ATOPIC DISorders in children may be associated with changes in types of childhood infections, vaccination programs, and intestinal microflora. People who follow an anthroposophic way of life use antibiotics restrictively, have few vaccinations, and consume many live lactobacilli, which may affect the intestinal microflora.

In a cross-sectional study, 295 children aged 5-13 years at two anthroposophic (or Steiner) schools near Stockholm, Sweden, were compared with 380 children of the same age at two neighboring schools. History of atopic and infectious diseases, use of antibiotics and vaccinations, and social and environmental variables were assessed. Skin prick tests were done for 13 common allergens, and blood samples from children and their parents were analyzed for allergen-specific serum IgE antibodies.

At the Steiner schools, 52% of the children had taken antibiotics in the past, compared with 90% in the control schools. Eighteen percent and 93% of children, respectively, had had combined immunization against measles, mumps, and rubella, and 61% of the children at the Steiner schools had had measles. Fermented vegetables containing live lactobacilli were consumed by 63% of the children at Steiner schools, compared with 4.5% at the control schools.

Skin-prick and blood tests showed that the children from Steiner schools had lower prevalence of atopy than controls (odds ratio 0.62 [95% CI 0.43-0.91]). There was an inverse relation between the number of characteristic features of an anthroposophic lifestyle and risk of atopy (P for trend = 0.01).

Prevalence of atopy is lower in children from anthroposophic families than in children from other families. Lifestyle factors associated with anthroposophy may lessen the risk of atopy in childhood.

COMMENT

Anthroposophy literally translated means wisdom and humanity of man. Promulgated by Rudolph Steiner in the early 20th century, anthroposophy is a phenomenological approach to the spirit, and holds a spiritual view of the world beginning with a capacity for thinking. This philosophy has been applied to education, architecture, art, agriculture, and medicine. In medicine, illness is regarded "as something intimately connected to the biography of the human being … not as a chance occurrence or mechanical breakdown."

In this study of medical outcomes, "Steiner units" were defined as no MMR vaccination; none of seven other vaccinations before age six months; antibiotics not more than twice and not before age two years; antipyretics not more than twice and not before age six months; consumption of fermented vegetables at least for a year, and consumption of mainly organic or biodynamically produced food in early childhood.

Children were evenly matched in baseline demographics, except that breast feeding in infancy was longer in Steiner children (5.7 months) than controls (4.3 months). Signs of atopy were assessed according to clinical exam (asthma, allergic rhinoconjunctivitis, atopic dermatitis, food allergy, and allergic urticaria), skin prick, and blood samples. The prevalence of wheeze in the last six months was 3.1% among Steiner children and 7.6% among controls; reported asthma diagnosed by a physician was 2.7% and 9.5%, and wheeze "ever" was 7.1% and 17.1%. Positive skin pricks prevalence was 7% and 13%; positive blood tests were 24% and 33% respectively. All these relationships were statistically significant.

The authors, largely from the

Karolinska Institute in Stockholm, are quick to point out that infectious diseases other than measles could also have been more frequent among the Steiner kids, and that a 1995 measles epidemic could have lowered the prevalence of atopy in Steiner kids. They could not identify a single specific factor responsible for the lower atopy.

Overuse of antibiotics in childhood is well-documented, and underuse of fruits and vegetables, fermented or not, is also well-documented among children and their parents. Avoiding MMR and other vaccinations, however, appears to be a different discussion.

Recommendation

Be open to patients who want to explore an anthroposophic approach—certainly to farming, which can yield delicious produce. The children of parents who elect to follow an anthroposophic medical lifestyle merit monitoring, as they may avoid common atopic and allergic diseases, now often treated with prescription medication. ❖

Well-done Red Meat and Breast Cancer Risk

Source: Zheng W, et al. Well-done meat intake and the risk of breast cancer. *J Natl Cancer Inst* 1998;90:1724-1729.

HETEROCYCLIC AMINES, MUTAGENS formed in meats cooked at high temperatures, have been demonstrated as mammary carcinogens in animals. A nested, case-control study among 41,386 cohort members of the Iowa Women's Health Study evaluated the potential role of heterocyclic amines and intake of well-done meat in the risk for human breast cancer.

A questionnaire was mailed to individuals who had breast cancer diagnosed during the period from 1992 through 1994 and a random sample of cancer-free cohort members to obtain information on usual intake of meats and on meat preparation practices. Color photographs showing various doneness levels of hamburger, beef steak, and bacon were included. Multivariate analysis was performed on data from 273 case subjects and 657 control subjects who completed the survey.

A dose-response relationship was found between doneness of meat consumed and breast cancer risk. The adjusted odds ratios (ORs) for very well-done meat vs. rare or medium-done meat were 1.54 (95% confidence interval [CI] 0.96-2.47) for hamburger; 2.21 (95% CI 1.30-3.77) for beef steak; and 1.64 (95% CI 0.92-2.93) for bacon. Women who consumed these three meats consistently very well-done had a 4.62 times higher risk (95% CI 1.36-15.70) than that of women who consumed the meats rare or medium. Risk of breast cancer was also elevated with increasing intake of well-done to very well-done meat.

Consumption of well-done meats and thus exposure to heterocyclic amines (or other compounds) formed during high temperature meat cooking may play an important role in the risk of breast cancer.

COMMENT

Put another brat on the fire! Here in Chicago, you can hear the backyard grillmeister next door man the tongs, shift the coals, and swear at the cat nearly every weekend and most weeknights. The grill is the one part of the kitchen in which most men feel truly at home, as it is usually not in the kitchen, but on the deck, in the backyard, by the shore, at the beach.

But what to do about the well-done crust, where evil lies? In this study, although frying, grilling, and barbecuing were only weakly correlated with the risk of breast cancer, well-doneness was highly correlated. And well-doneness can come from any of these cooking methods—plus roasting, deep frying, even sautéing.

This is strong, comprehensive, epidemiological case-control data. More than 41,000 Iowa women, aged 55-69, have been assessed for cancer risk and prevalence since they returned a mailed questionnaire in January 1986. No information was collected then about meat or its usual doneness, so the investigators performed a case-control study from 1995-1996. The investigators, from the Universities of Minnesota and Iowa and the National Cancer Institute, included chicken and fish with the definition of meat, but the correlation was with red meat.

Recommendations

Tell your patients who want to reduce their risk for breast cancer to cook or order their burgers and steak medium or rare, and to send them back or do it over if overdone. This is even more important than reducing red meat intake. If patients or the grillmeister want a good crust, use cracked spices (e.g., peppercorns or cumin seeds) and whole seeds (e.g., sesame or pumpkin) pressed into the meat. These will add extra flavor, so much so that you won't miss the nearly burned char. ❖

In Future Issues:

Valerian for Insomnia

Black Cohosh for Menopausal Symptoms

Omega-3 Fatty Acids for Stroke Prevention

Music Therapy as an Anxiolytic